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PRINCIPAL INVESTIGATOR: Roberta F. White, Ph.D.

CONTRACTING ORGANIZATION: Boston University
Boston, Massachusetts 02118

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Roberta F. White, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Boston University
Boston, Massachusetts 02118

E-Mail: rwhite@bu.edu

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The specific aims of this project were 1) to determine whether objective test measures reveal any progressive diminution in cognitive function among the GW-era veterans who participate in the study in 1995-1998 (Time 1) by comparing test performance observed initially to performance 4-5 years later and 2) to determine whether any identifiable declines in function are related to exposures experienced during deployment to the Gulf, post-traumatic stress disorder, major depressive disorder, or existence of multiple health complaints.

Participants were deployed and non-deployed GW-era veterans who were tested at Time 1. The GW-deployed group included patients initially referred for clinical neuropsychological evaluations and a group of individuals seeking treatment or diagnostic evaluation for any purpose. Controls were treatment-seeking non deployed GW-era veterans studied between 1995-1998.

The prior finding of differences between the deployed and non-deployed treatment seeking GW-era veterans in neuropsychological outcomes was not supported by the Time 2 data. This may reflect spurious findings at Time 1 or selection bias in the non-deployed group (high rates of major depression). The deployed veteran group did not perform worse at Time 2 than Time 1 suggesting that there was no progressive cognitive decline associated with GW deployment.

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5. INTRODUCTION

Prior research completed at the Boston Environmental Hazards Center (BEHC) indicated that Gulf War (GW) era veterans deployed to the Gulf scored more poorly on a limited, specific group of neuropsychological test measures including attention, visuoconstruction and visual memory when compared with GW-era non-deployed veterans (Time 1, 1995-1998; Sullivan et al., 2003). These findings raised the possibility of subtle, "subclinical" central nervous system (CNS) damage associated with Gulf deployment. The etiology of the neuropsychological deficits was unclear, but published BEHC studies suggested that they may be related to environmental exposures experienced in the Gulf (Sullivan et al. 2003; White et al., 2001; 2003). These studies also suggested that the neurocognitive status of GW veterans could not be attributed solely to stress, psychiatric status, or compensation seeking (White et al., 2001; 2003).

Clinical experience with GW-era veterans who were deployed to the Gulf indicated that many veterans reported that their cognitive functioning worsened over the time since their return. Specifically, study veterans from a prior study of GW-era veterans (Time 1) reported functional declines in the areas of short-term memory and concentration. Self-reports of declines are at odds with the usual course of CNS effects of exposure to neurotoxicants, which generally remit or remain static in the absence of exposure.

The specific aims of this project were 1) to determine whether objective test measures revealed any progressive diminution in cognitive function among the participants in the Time 1 study by comparing test performance observed initially to performance 4 – 5 years later and 2) to determine whether any identifiable declines in function were related to exposures experienced during deployment to the Gulf, post-traumatic stress disorder, major depressive disorder, or existence of multiple health complaints.

6. BODY

Subjects and methods:

Overview

Deployed and non-deployed GW-era veterans who were tested in a prior study conducted by the PI (Time 1, 1995-1998) were the participants in this study. The GW-deployed group included patients who were initially referred for clinical neuropsychological evaluations and a group of individuals who were seeking treatment or diagnostic evaluation for any purpose. Controls were non-deployed GW-era veterans studied between 1995-1998 (also treatment-seekers). Test scores, target diagnoses, and health symptoms for individuals who were deployed to the Gulf were compared to the same outcomes for those who were not deployed. Additionally, longitudinal analyses of difference scores were conducted in order to document changes over time. The assessment instruments used at Time 1 were repeated.

Study Sample at Time 1 (Treatment Seekers)

1. *Participants tested for baseline study protocol at Time 1*: All treatment seeking veterans from the VA Boston Healthcare System (VABHS) who were in the military during the time of the GW (1990-1991) were considered to be potential study participants at Time I. The personnel involved in the recruitment of participants were not aware of the status of potential participants with regard to deployment to the Gulf, and steps were taken to reduce the likelihood that this information would become known to project staff during the recruitment process. The study coordinator did not have access to information such as the clinic from which each potential participant was drawn.

a. GW-deployed treatment seekers. These participants came from two sources. The first group was recruited from a list generated and periodically updated by the supervisors of outpatient clinics. This list included all GW-era veterans attending any clinics (except substance abuse) at the VABHS Jamaica Plain facility, the Causeway Street (Boston) out-patient clinic, and the Lowell, MA, facility. A total of 87 veterans

who had been deployed to the Gulf were recruited from this source. The second source of treatment seeking GW-deployed veterans came from referrals to the Neuropsychology Service of the VABHS from clinics and facilities in VISN I (N=120). The total GW-deployed treatment-seeking sample was 207.

b. Non-GW-deployed treatment seekers. These controls were recruited from the same list generated by the outpatient clinic supervisors of all treatment seeking GW-era veterans. Fifty-three patients, who were in the military but were not GW-deployed, participated.

2. *Participants at Time 2.* One hundred eleven participants were examined in three years. Study participants were recruited on the basis of the original test date and were tested approximately 4 years (+/- 6 months) after the last neuropsychological evaluation. Response rates are discussed on page 13.

Table 1: Participants: GW-era Treatment Seekers

	Time 1	**Time 2**
GW Deployed	207	90 *
Non-deployed	53	21 **
Total	260	111

* 43% of Time 1 sample ** 40% of Time 1 sample

b. Initial Contact. The first contact with participants was by telephone (or by mail, if there was no telephone number available). The initial contact consisted of a description of the project, including types of assessment, time required, and financial reimbursement for study participation. Participants had an opportunity to ask questions about the procedure. They were informed that choice or non-choice to

participate in the project would have no bearing on their medical care and that, if they chose to participate, they could withdraw at any time without prejudice. Those consenting to participate were asked questions to determine whether they met preliminary inclusion criteria for the study. Exclusion criteria included current treatment for alcohol or other substance abuse, sensory or motor impairments precluding use of the computer, and serious brain injury prior to the GW era. Prior substance abuse and current medications were recorded but did not constitute exclusion criteria. An appointment at the VABHS was scheduled for individuals agreeing to participate.

c. Assessment instruments and procedures.

The assessment instruments employed in the current study were those utilized in prior studies of GW veterans conducted by the PI including the Time 1 evaluation of the current study sample (1995-98; Sullivan et al., 2003). They included a questionnaire that queried information about environmental exposures, a psychological assessment with a semi-structured clinical interview, and a neuropsychological evaluation. The protocol usually required 2 - 3 hours for completion and was most often completed during one visit.

As part of a questionnaire, participants were asked questions about school achievement and occupational history (including possible occupational exposure to neurotoxicants), family history of psychiatric disorder, and post-deployment stressors.

The psychological interviews and semi-structured clinical interview were administered by a clinical psychologist (Dr. Krengel). They included the Structured Clinical Interview for DSM-IV (SCID; Spitzer et al., 1990), the Clinician Administered PTSD scale (CAPS-DX; Blake et al, 1995) and a semi-structured clinical interview. The SCID is used to determine Axis I psychiatric disorders and has been shown to be reliable (Wolfe & Keane, 1993). The CAPS-DX is a state-of-the-art instrument for confirming the diagnosis of current and/or lifetime PTSD, as well as for evaluating the intensity, frequency and severity of the disorder and its individual symptom criteria. The semi-structured clinical

interview elicited information pertaining to current or past mood disorders, substance abuse, neurological and medical illness, traumatic brain injury, history of other traumatic events, birth trauma, developmental delays, and history of learning disability.

The neuropsychological test battery (see Table 2) was administered by trained professionals who were blind to the status of the participants' diagnoses and exposure status. The battery was chosen from a more extensive battery that has been employed extensively by the PI in prior work with persons being assessed for brain damage from environmental or occupational exposure to neurotoxicants (White & Proctor, 1992). All of the tests have reliable psychometric properties and have been widely used for both research and clinical purposes. The tests were drawn from two major categories: (1) tests tapping relatively stable premorbid cognitive/intellectual abilities and (2) tests that have been shown to have high specificity and sensitivity for detecting changes in localized or diffuse cognitive brain functions. Tests in the first category provided uniform estimates of baseline abilities for all individuals; the more specialized tests assessed functions that may be differentially affected by a particular disease or condition (Lezak, 1995).

Table 2. Full Neuropsychological Test Battery

	Test Name	Description
I.	Tests of General Intelligence	
1.	Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) Information subtest	Information usually learned in school; to assess native intellectual abilities
II.	Tests of Attention, Vigilance, and Tracking	
1.	Digit Span Subtests: WAIS-R Wechsler Memory- Scale-Revised (WMS-R; Wechsler, 1987)	Oral recall of digits forward and backward; given twice to assess consistency of performance
2.	Trail-making Test (Reitan & Wolfson, 1985)	Timed connect-a-dot task to assess attention and motor control requiring sequencing (A) and alternating sequences (B)
3.	Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977)	Continuous addition test; to assess sustained attention under distracting conditions
4.	Wisconsin Card Sorting Test (WCST; Heaton et al, 1993)	Task requiring use of feedback to infer decision making rules; assesses problem solving ability and flexibility (64 cards only)
III.	Tests of Motor Function	
1.	Finger Tapping Test (Reitan & Davidson, 1974)	Speed of tapping with index finger of each hand; assesses simple motor speed
2.	Purdue Pegboard Test (Purdue Research, 1948)	Speed of inserting pegs into slots using each hand separately and both together; assesses dexterity
IV.	Tests of Visuospatial Function	
1.	WAIS-R Block Design	Replication of 2-dimensional designs using blocks ; assesses Visuoconstruction
2.	Hooper Visual Organization Test (HVOT; Hooper,1958)	Identification of objects from line drawings of disassembled parts; assesses ability to synthesize visual stimuli

V. Tests of Memory

1. Paired Associate Learning-WMS-R	Recall of second member of pairs of words immediately and after a delay; assesses verbal short-term memory (learning and retention)
2. Visual Reproductions-WMS	Reproductions of visual designs, immediately and a delay; assesses visuospatial short-term memory (learning and recall)
3. California Verbal Learning Test (CVLT; Delis et al.,1987)	List of 16 nouns from 4 categories presented over multiple learning trials with recall after interference

VI. Tests of Personality and Mood

1. 1. Profile of Mood States (POMS; McNair et al., 1971)	65 single-word descriptors of affective symptoms endorsed for degree of severity and summed on six mood scales

VII. Tests of Motivation

1. Test of Memory Malingering (TOMM; Tombaugh, 1996)	Simple task requiring immediate forced choice recognition of line drawings of 50 common objects; assesses effort

d. Data collection: For the 3 years of data collection, the following numbers of participants were recruited and completed the protocols.

Table 3: Study Participant Testing at Time 2

Year	GW –Deployed	Non-Deployed
1	41	3
2	37	10
3	12	8
Totals	90	21

A total of 111 treatment-seeking veterans participated in this study. Gulf-deployed veterans totaled 90, and non-deployed-GW-era treatment seeking veterans totaled 21. An additional 15 subjects who had been scheduled failed to show for appointments.

Non-responders:

Of 260 possible participants, 229 were contacted either by mail or by phone and 31 were unreachable or could not be located. A total of 111 veterans participated in the follow-up study. Most potential participants who refused to participate reported that they did so because of scheduling conflicts. However, only 12 study participants who were lost to follow-up were still seeking healthcare services at the VABHS, while the remaining group (n = 137) had had no contact with the VISN 1 VA healthcare system since their initial Time 1 testing. Additionally, four study participants from the initial Time 1 group were deceased (3 GW-deployed, 1 non-deployed) and 48 relocated out of state (beyond VISN 1 range and above allotted travel expense). Demographic information comparing responders and non-responders is presented in Table 4.

Table 4a: Comparison of responders and non-responders at Time 2 on demographic and Time 1 data

	GW		Control	
	Responders	Non-respond	Responders	Non-respond
	(n = 90)	(n = 104)	(n =21)	(n = 32)
Age	36.5	35.1	34.7	29.1
Education	13.3	13.6	13.7	13.9
Gender (% female)	14%	9%	35%	14%
Major Depression	5%	6%	5%	0%
Post-Traumatic Stress Disorder (PTSD)	16%	15%	10%	9%
Multiple Chemical Sensitivity	3%	2%	0%	0%
Chronic Fatigue Syndrome	3%	<1%	0%	3%
WAIS-R information	19.1 (5.1)	19.0 (5.1)	20.1 (4.2)	18.7 (5.6)
WAIS-R Digit Span Forward	6.6 (1.3)	6.6 (1.3)	6.9 (1.2)	7.4 (1.3)
WAIS-R Digit Span Backward	5.1 (1.6)	5.1 (1.4)	4.5 (1.7)	5.7 (1.4)**
WAIS-R Block Design	10.2 (2.4)	10.4 (2.5)	11.1 (2.6)	11.7 (2.6)
WMS-R Visual Reproductions	8.8 (3.1)	9.2 (3.5)	10.4 (3.4)	11.0 (2.9)
Rey-Osterreith Complex Figure Test	20.5 (5.6)	21.1 (6.0)	23.6 (7.1)	24.3 (5.9)

Separate analyses compared responders to non-responders in the GW and Control samples, using the t-test for measurement factors and the Chi-square test (or Fisher's test when samples are small) for categorical factors. Significant differences between responders and non-responders are indicated by * for p<.05, ** for p<.01, and *** for p<.001.

To assess whether study responders and non-responders differed on important demographic variables, medical and psychiatric diagnoses and key neuropsychological measures from the Time 1 testing, separate analyses were performed to compare responders to non-responders for the GW and control groups. Results showed that responders did not differ significantly from non-responders in the GW or control groups for any demographic, psychiatric or medical diagnosis. The only statistically significant

difference between responders and non-responders was the WAIS-R Digit Span backward test score, with control responders performing significantly worse than non-responder controls ($p < .01$) at Time 1.

Table 4b. Time 1 differences on Neuropsychological measures, for the overall Time 1 sample and the sample followed at Time 2.

	Overall Time 1 Sample			Sample followed at Time 2		
	GW	Control	p-value	GW	Control	p-value
	(n=207)	(n=53)		(n=90)	(n=21)	
WAIS-R Digit Span Forward	6.6 (.01)	7.2 (.18)	.008	6.5 (1.4)	6.5 (1.2)	.23
WAIS-R Digit Span Backward	5.1 (.11)	5.4 (.22)	.008	5.4 (1.4)	5.0 (1.4)	.32
WAIS-R Block Design	10.3 (.17)	11.6 (.35)	.01	11.0 (2.8)	10.5 (2.7)	.04
WMS-R Visual Reproductions-Delayed Recall	9.0 (.25)	10.9 (.41)	.007	8.8 (3.1)	10.4 (3.4)	.05
Rey-Osterreith Complex Figure Delayed Recall	20.8 (.50)	24.3 (.86)	.009	20.5 (5.6)	23.6 (7.1)	.05

In order to assess for response bias, Time 2 study respondents were compared on their Time 1 performances with the Time 1 *overall* study sample. Statistically significant differences were found in the Time 2 responders on their Time 1 performances in three of the five significant cognitive tests from the overall Time 1 study sample. Specifically, the domains of visuoconstruction and retention of visual information were significantly different in the study responder group. Overall, these findings suggest similar performances in the responder and non-responder groups at Time 1, although the overall sample likely had more power to detect subtle differences than the smaller subgroup of Time 2 responders.

Data analyses and results. Listed by hypotheses from initial grant proposal:

Preliminary Analysis:

GW-deployed Time 2 study responders showed a slight non-significant increase in diagnosis of post-traumatic stress disorder (PTSD) from Time 1 to Time 2 testing (16% to 21%, p = .344 by McNemar's dependent sample chi-square test). The non GW-deployed responders showed no significant increase in PTSD at Time 2 and remained at 10% incidence (p = 1.00 by McNemar's dependent sample chi-square test). Additionally, GW-deployed Time 2 study responders showed a non-significant increase in major depressive disorder (MDD) between the two test periods, increasing from 8% (n = 7) to 14% (n = 13, p = .727 by McNemar's dependent sample chi-square test). The control group study responders also showed a non-significant increase in major depressive disorder diagnosis, increasing from 5% (n = 1) to 24% (n = 5, p = .500 by McNemar's dependent sample Chi-square test) between the two test periods. Result of study responder demographics at Time 1 between GW-deployed and non-deployed veterans are shown in Table 5.

Table 5. Responder Demographics at Time 1

	GW Deployed (n = 90)	Non-deployed (n =21)	p-value
Age (mean)	36.5	34.7	.427
Education	13.3	13.7	.438
Gender (% female)	14%	35%	.037
Major Depression	8%	5%	.427
PTSD	16%	10%	.287
Chronic Fatigue Syndrome	3%	0%	.171
Multiple Chemical Sensitivity	3%	0%	.171

Analyses compared GW and Control samples, using the t-test for measurement factors and the Chi-square test (or Fisher's test when samples are small) for categorical factors.

When comparing study responder demographics at Time 1 between GW deployed and non-deployed veterans by t-test or Chi-square test, the only significant difference was found for gender (35% vs. 14%, p = .037) with the non-deployed group showing a higher number of women than the GW-deployed group.

Power Analyses: Analyses of change in neuropsychological performance from Time 1 to Time 2 are based on 90 GW-deployed and 21 non-GW-deployed veterans. Given these sample sizes, our analyses comparing mean change in GW versus non-GW deployed veterans have 80% power of detecting a difference corresponding to an effect size of 0.68, where the effect size is the difference in mean change scores between the two groups divided by the pooled standard deviation of change scores.
This corresponds to a medium to large effect in the language of Cohen (J Cohen, 1988). This effect size corresponds to roughly a 6.8 average change on POMS t-scores for GW relative to non-GW-deployed veterans (change scores on the POMS have a standard deviation of roughly 10 in our sample); a 1.3 average change on the Digit Span (forward or backward, with a standard deviation of about 2.0); or an average change of 2.0 on the Purdue Pegboard (standard deviation of about 3.0). Smaller differences between GW deployed and non-deployed veterans may not be detected by our study, largely due to the smaller number of non-GW-deployed veterans in our study. Tables 6a, 6b and 6c further explore analyses of change in neuropsychological performance in GW and non-GW deployed veterans.

1. Hypothesis 1. It was predicted that there would be a progressive diminution in cognitive functioning in GW deployed treatment-seeking veterans at Time 2 compared with initial baseline testing approximately four years previously (Time 1) in the domains of attention, motor function and short-term memory. To test this hypothesis, an independent sample t-test was performed to compare the mean change (Time 2 – Time 1) for each variable of interest. Results appear in Table 6a.

Table 6a. Comparison of GW and Control groups on change in Neuropsychological performance from Time 1 to Time 2 (Mean (SD) change)

Domain	GW (n=90)	Control (n=21)	p-value
Attention/ Executive system			
Trails A (time)	-.92 (9.9)	-1.6 (11.4)	.793
Trails B (time)	-2.3 (36.9)	-7.2 (36.5)	.625
Digit Span forward (raw)	-.22 (1.6)	-.30 (1.9)	.846
Digit Span Backward (raw)	-.61 (1.9)	-.15 (2.1)	.347
Wisconsin Card Sort (# sorts)	.05 (1.5)	.20 (1.3)	.689
PASAT Trials 1-4	4.0 (19.4)	15.6 (18.6)	.057
Motor and visuomotor			
Finger Tap Test (dominant)	-.79 (8.2)	.57 (10.1)	.526
Finger Tap Test (nondominant)	-.78 (7.9)	-.28 (8.5)	.807
Purdue Pegboard (dominant)	-1.1 (2.8)	-2.7 (3.9)	.066
Purdue Pegboard (non-dominant)	-.64 (2.9)	-3.6 (3.8)	.001
Block Design	1.3 (6.2)	-3.5 (6.1)	.002
Memory			
CVLT (trials 1-5)	.21 (13.8)	3.3 (10.1)	.345
CVLT - long delay (# correct)	.27 (2.2)	.43 (2.6)	.216
WMS Verbal PAL hard delay	.07 (1.4)	.10 (.64)	.938
WMS Visual Reproductions delay	.80 (2.8)	.30 (2.7)	.478
Mood			
POMS tension t-score	-3.3 (8.5)	-1.7 (10.8)	.460
POMS depression t-score	-.77 (11.6)	-2.1 (11.2)	.648

POMS Anger t-score	-1.5 (11.0)	.60 (9.9)	.435
POMS vigor t-score	-3.1 (9.8)	-7.9 (19.8)	.086
POMS fatigue t-score	.55 (9.8)	-2.3 (14.2)	.310
POMS confusion t-score	-1.7 (9.0)	-.30 (9.8)	.551

* Change scores calculated as the Time 2 value minus the Time 1 value, so a positive change indicates an increase in the measure over time, and a negative change indicates a decrease in the measure over time.

When mean change scores were analyzed between Gulf-deployed and control responders, significant differences were found in the domains of motor and visuo-motor skills, specifically on the Purdue Pegboard non-dominant hand (p = .001) and the Block Design test (p = .002). However, the controls decreased more over time on these test items than the GW-deployed responders. The PASAT test from the domain of executive functions approached significance between the groups (p = .057). Overall, significant declines were seen on two of out 21 outcomes.

Table 6b. Hypothesis 1. Paired T-tests Gulf War-deployed Veterans (N= 90)

Domain	Time 1 Mean (SD)	Time 2 Mean (SD)	Change* Mean (SD)	p-value
Attention/ Executive system				
Trails A (time)	32 (11.4)	31.1 (10.3)	-.92 (9.9)	.402
Trails B (time)	78.8 (43.3)	76.0 (40)	-2.3 (36.9)	.484
Digit Span forward (raw)	8.1 (2.1)	7.9 (2.2)	-.22 (1.6)	.240
Digit Span Backward (raw)	7.0 (2.6)	6.4 (2.4)	-.61 (1.9)	.006
Wisconsin Card Sort (# sorts)	3.3 (1.3)	3.4 (1.3)	.005 (1.5)	.773
PASAT Trials 1-4	117.8 (30.4)	121.8 (34.8)	4.0 (19.4)	.153

Motor and visuomotor				
Finger Tap Test (dominant)	48.9 (9.1)	48.1 (8.9)	-.79 (8.2)	.337
Finger Tap Test (nondominant)	44.7 (8.4)	43.9 (8.0)	-.78 (7.9)	.373
Purdue Pegboard (dominant)	14.2 (2.4)	13.1 (2.3)	-1.1 (2.8)	.005
Purdue Pegboard (non-dominant)	13.5 (2.1)	12.9 (2.8)	-.64 (2.9)	.101
Block Design	30.3 (8.8)	31.6 (9.5)	1.3 (6.2)	.066
Memory				
CVLT (trials 1-5)	51.1 (10.7)	50.9 (15.1)	-.21 (13.8)	.886
CVLT - long delay (# correct)	10.8 (3.2)	10.5 (3.6)	-.27 (2.2)	.278
WMS Verbal PAL hard delay	3.1 (1.1)	3.0 (1.3)	-.07 (1.4)	.634
WMS Visual Reproductions delay	8.9 (3.1)	9.7 (3.0)	.80 (2.8)	.015
Mood				
POMS tension t-score	46.4 (9.2)	43.1 (9.5)	-3.3 (8.5)	.001
POMS depression t-score	44.1 (10.5)	44.9 (8.4)	-.77 (11.6)	.566
POMS Anger t-score	50.08 (9.6)	48.6 (11.0)	-1.5 (11.0)	.232
POMS vigor t-score	52.9 (8.9)	50.2 (9.5)	-3.1 (9.8)	.010
POMS fatigue t-score	54.4 (8.9)	54.7 (11.2)	.55 (9.8)	.63
POMS confusion t-score	49.1 (8.3)	47.1 (10.2)	-1.7 (9.0)	.110

Table 6c. Hypothesis I. Paired T-test comparison of non-deployed Control Veterans (n = 21).

Domain	Time 1 Mean (SD)	Time 2 Mean (SD)	Change* Mean (SD)	p-value
Attention/ Executive system				
Trails A (time)	29.8 (11.1)	28.2 (9.2)	-1.6 (11.4)	.534

Trails B (time)	79.7 (42.3)	72.5 (18.3)	-7.2 (36.5)	.375
Digit Span forward (raw)	8.6 (2.1)	8.3(1.9)	-.30 (1.9)	.487
Digit Span Backward (raw)	5.9 (1.9)	6.3 (2.5)	-.15 (2.1)	.751
Wisconsin Card Sort (# sorts)	4.0 (1.0)	4.1 (1.3)	.20 (1.3)	.494
Motor and visuomotor				
Finger Tap Test (dominant)	49.6 (9.5)	50.1 (7.1)	.57 (10.1)	.803
Finger Tap Test (nondominant)	44.8 (8.1)	44.5 (8.5)	-.28 (8.5)	.887
Purdue Pegboard (dominant)	15.1 (3.2)	12.4 (2.5)	-2.7 (3.9)	.015
Purdue Pegboard (non-dominant)	15.1 (2.5)	11.5 (3.7)	-3.6 (3.8)	.002
Block Design	33.1 (9.3)	29.6 (11.2)	-3.5 (6.1)	.017
Memory				
CVLT (trials 1-5)	56.3 (9.0)	53.0 (9.8)	-3.3 (10.1)	.154
CVLT - long delay (# correct)	11.3 (2.7)	11.7 (3.0)	.43 (2.6)	.452
WMS Verbal PAL hard delay	3.3 (1.8)	3.4 (.93)	.10 (.64)	.494
WMS Visual Reproductions delay	10.4 (3.3)	10.7 (2.8)	.30 (2.7)	.629
Mood				
POMS tension t-score	42.3 (9.4)	40.6 (11.6)	-1.7 (10.8)	.504
POMS depression t-score	43.6 (9.8)	41.5 (11.9)	-2.1 (11.2)	.413
POMS Anger t-score	47.0 (6.5)	47.6 (12.3)	.60 (9.9)	.790
POMS vigor t-score	55.8 (10.5)	47.9 (14.8)	-7.9 (19.8)	.028
POMS fatigue t-score	49.1 (9.4)	46.9 (16.4)	-2.3 (14.2)	.489
POMS confusion t-score	44.7 (8.9)	44.4 (9.5)	-.30 (9.8)	.892

* Change scores calculated as the Time 2 value minus the Time 1 value, so a positive change indicates an increase in the measure over time, and a negative change indicates a decrease in the measure over time.

The GW-deployed responders showed a statistically significant mean change in performance (Time 2 – Time 1) on three measures, Digit Spans backward, Purdue Pegboard (dominant hand), and visual reproductions delay. The GW-responders showed a decreased mean performance over time for the Purdue pegboard and the Digit spans test and an improved performance for the visual memory task (Weschler Memory Scale Visual Reproductions delayed recall). Significant change scores were also found for the mood measures of POMS tension and vigor (Table 6b), with the GW-veterans reporting less tension and less vigor over time.

The control responders showed significantly decreased mean performance on three test measures, the Purdue pegboard (dominant and non-dominant hands), and block design. They also repeated less vigor on the POMS vigor score.

These data suggest relatively static overall performances in GW veterans on test-retest measures with a four-year time interval. Overall, deployed veterans showed statistically significant declines on only two of out 15 cognitive measures, with improvement on one out of 15. There was improvement on one out of six mood measures and decline on one out of six. For controls, statistically significant declines were seen for three out of 15 cognitive outcome scores and diminished mood was seen on one out of six mood measures, with no statistically significant improvements. These findings do not support global diminution of performances on neuropsychological measures over time.

2. Hypothesis 2. It was predicted that the treatment-seeking GW-deployed veterans would continue to be impaired relative to the non-deployed treatment seeking controls in the neuropsychological domains of motor skills, mood and memory. To test this hypothesis, an analysis of covariance was performed between GW-deployed veterans and non-GW-deployed controls on mean change scores controlling for age, gender and education.

Table 7. GW-deployed Veterans vs. Non-GW-deployed Veterans, on change from Time 1 To Time 2 (Controlling for Age, Education, and Gender)

	Gulf War Deployed (N = 90) Change Mean (SD)	Non-Deployed Controls (N = 21) Change Mean (SD)	p-value
Attention & Executive System			
WMS-R Digit Span raw, forward	-.22 (1.6)	-.30 (1.9)	.775
WMS-R Digit Span raw, backward	-.61 (1.9)	-.15 (2.1)	.427
WCST, # of sorts	.005 (1.5)	.20 (1.3)	.802
Trail-Making A (time)	-.92 (9.9)	-1.6 (11.4)	.076
Trail-Making B (time)	-2.3 (36.9)	-7.2 (36.5)	.213
PASAT Trials 1-4	4.0 (19.4)	15.6 (18.6)	.028
Motor/Psychomotor Abilities			
Finger Tapping, dominant	-.79 (8.2)	-.57 (10.1)	.870
Finger Tapping, non-dom.	-.78 (7.9)	-.28 (8.5)	.330
Purdue Pegboard, dominant hand	-1.1 (2.8)	-2.7 (3.9)	.332
Purdue Pegboard, non-dominant hand	-.64 (2.9)	-3.6 (3.8)	.060
Visuospatial Constructional Abilities			
WAIS-R Block Design, raw	1.3 (6.2)	-3.5 (6.1)	.029
Memory			
CVLT, Trials 1-5, # correct	.21 (13.8)	3.3 (10.1)	.810
CVLT, LDFR, # correct	.27 (2.2)	.43 (2.6)	.894
WMS-R Verbal PAL, hard items, delay	.07 (1.4)	.10 (.64)	.715
WMS Visual Reproduction, delayed	.80 (2.8)	.30 (2.7)	.213
Mood			
POMS tension *t* score	-3.3 (8.5)	-1.7 (10.8)	.785
POMS depression *t* score	-.77 (11.6)	-2.1 (11.2)	.689
POMS anger *t* score	-1.5 (11.0)	.60 (9.9)	.908
POMS fatigue *t* score	-3.1 (9.8)	-7.9 (19.8)	.783
POMS confusion *t* score	.55 (9.8)	-2.3 (14.2)	.646

Results of an analysis of covariance controlling for age, gender and education showed statistically significant differences in two neuropsychological test outcome measures between the groups on mean change scores (Time 2 – Time 1). Of the two significantly different test outcomes, scores on the PASAT test improved in both the GW-deployed and control groups, but the control group improved to a

significantly greater degree. The block design test results were also significantly different between the groups over time, with GW-deployed veterans showing improved mean performance over time while the control group showed a decrease in mean performance over time.

3. Other analyses

(a). Among veterans tested at both Times 1 and 2, the rates of the following diagnostic outcomes were compared: post-traumatic stress disorder (PTSD), major depressive disorder (MDD), multiple chemical sensitivity (MCS) and chronic fatigue syndrome (CFS). The rate of PTSD at Time 2 was 21% (N= 19, total = 90) for GW-deployed veterans, while the rate of PTSD in non-deployed veterans tested twice remained at 10% (N = 2, total =21). This difference was not statistically significant. In addition, rate of MDD was slightly lower in the GW-deployed group (15%, n = 13, total=90) than the non-deployed group (24%, n = 5, total =21). This difference was not statistically significant. Rates for CFS and MCS remained the same as they had at Time 1, at less than 3% for each diagnosis in both groups.

(b). In terms of health symptom reporting, it was expected that GW-deployed veterans would report similar current health symptoms at Time 2 compared as they had at Time 1. Tables 8 shows data from a health symptom checklist questionnaire that was given to participants at both Time 1 and Time 2 the questionnaire evaluated the number of dichotomous (yes / no) responses for each health symptom variable. Change in symptom reporting is shown and p-values for the percent change in symptom reporting between testing cycles is reported.

Table 8: Changes in report of health symptoms from Time 1 to Time 2

Symptom	GW (n=90)			Controls (n=21)			GW vs. Control p-value
	Time 1	Time 2	Change	Time 1	Time 2	Change	
Aches and Pains	45%	77%	+32%	21%	36%	+15%	.029
Joint pain	54%	88%	+34%	31%	29%	-2%	.024
Headaches	68%	78%	+10%	64%	43%	-21%	.281
Skin rash	48%	62%	+14%	15%	21%	+7%	.142
Fatigue	72%	88%	+16%	36%	64%	+28%	.069
Nausea	48%	59%	+11%	21%	31%	+10%	.310
Forgetfulness	72%	81%	+9%	44%	58%	+14%	.576
Concentration	54%	74%	+20%	43%	57%	+14%	.979
Confusion	33%	55%	+22%	25%	23%	-2%	.649

Results comparing change scores in health symptom reporting between GW-deployed veterans and controls showed significant differences for the symptoms of aches and pains and joint pain with GW veterans reporting higher percentage of change than the non-deployed veterans. Specifically, the GW veterans showed a 32% increase in reporting of aches and pains while the control responders showed a 15% increase in this health symptom. For joint pain, the GW-deployed responders showed a 32% increase in symptom reporting while the controls showed a 2% decrease in symptom reporting over this time period. Statistically significant differences were thus seen in two out of nine outcome measures.

(c). Possible etiologies of CNS findings in GW-deployed veterans that have been raised in prior research include exposure to pyridostigmine bromide (PB) (Almog, 1991; Friedman et al., 1996; Sullivan et al., 2003), pesticide use (Moss, 2001), location near the Khamisiyah weapons depot during the war (McCauley et al., 2001), PTSD (Vasterling et al., 1997), and mood disorders (Sillanpaa et al., 1997). A comparison of mean change scores with two independent sample t-tests showed no significant

differences for pesticide exposure or PTSD diagnosis. However, GW veterans with Khamisiyah notification (n=23) showed a significant difference in visual reproductions delayed change score (mean change / SD -.32 (3.2), p=.049) performing significantly worse over time compared with non-Khamisiyah notified GW veterans (n = 77).

Data shown in Table 9 reflect findings in the GW-deployed group among participants with and without self-reported exposure to PB using mean change scores and employing two independent sample t-tests. Results of this analysis found that GW veterans with self-reported PB exposure (n = 28) performed better on the mean block design test (p = .048) and on the anger scores on the Profile of Mood Scales (p = .020).

Table 9. Change in Neuropsychological performance from Time 1 to Time 2, self-reported PB exposure, Gulf-deployed veterans

Domain	PB-Exposed (n=28)	Non-Exposed (n=62)	p-value
Trails A (time)	-1.9 (7.9)	-.57 (7.7)	.539
Trails B (time)	-3.2 (20.6)	-3.2 (34.2)	.999
Digit Span forward (raw)	-.33 (1.6)	-.11 (1.5)	.598
Digit Span Backward (raw)	-1.0 (2.0)	-.11 (2.1)	.135
Finger Tap Test (dominant)	-.32 (7.1)	-2.2 (10.2)	.431
Finger Tap Test (nondominant)	-.35 (6.6)	-1.3 (10.1)	.689
Purdue Pegboard (dominant)	-1.1 (2.5)	-.71 (2.4)	.663
Purdue Pegboard (non-dominant)	-.75 (2.4)	-.71 (2.6)	.966
Block Design	3.1 (5.3)	-.14 (6.4)	.048
CVLT (trials 1-5)	1.6 (15.1)	-3.1 (13.1)	.265
WMS Visual Reproductions delay	1.2 (2.8)	1.0 (2.1)	.519

POMS tension t-score	-1.9 (6.4)	-5.6 (8.7)	.098
POMS depression t-score	.32 (8.2)	-2.3 (13.8)	.407
POMS Anger t-score	1.2 (9.1)	-5.3 (9.7)	.020
POMS fatigue t-score	2.2 (8.4)	-2.0 (8.3)	.082
POMS confusion t-score	-.43 (6.8)	-3.1 (8.1)	.218

Gulf War veterans with self-reported PB exposure showed significantly different change scores than non-exposed GW-veterans on two out of 16 outcome measures, with one measure showing improved scores in the exposed group (block design test) suggesting that these results may be due to chance. No significant interaction effects were found among the Khamisiyah, pesticide and PB exposures.

Table 10. Change in Neuropsychological performance from Time 1 to Time 2, Major Depressive Disorder diagnosis, Gulf-deployed veterans

Domain	MDD (n=13)	Non-MDD (n=64)	p-value
Trails A (time)	2.3 (13.0)	-2.1 (9.8)	.165
Trails B (time)	-10.3 (76.3)	-2.1 (23.0)	.707
Digit Span forward (raw)	-.66 (2.1)	-.21 (1.5)	.385
Digit Span Backward (raw)	.33 (1.6)	-.84 (1.8)	.049
Finger Tap Test (dominant)	4.2 (9.9)	-1.8 (7.1)	.018
Finger Tap Test (nondominant)	4.7 (8.6)	-1.7 (7.5)	.009
Purdue Pegboard (dominant)	-1.1 (4.6)	-1.0 (2.4)	.937
Purdue Pegboard (non-dominant)	1.1 (2.4)	-.75 (2.8)	.081
Block Design	-.23 (7.9)	1.0 (5.9)	.522
CVLT (trials 1-5)	1.2 (25.2)	-.98 (11.3)	.632
WMS Visual Reproductions delay	.75 (2.4)	.54 (2.8)	.819

POMS tension t-score	.38 (6.5)	-4.1 (8.9)	.095
POMS depression t-score	5.8 (12.9)	-1.8 (11.4)	.039
POMS Anger t-score	3.3 (7.1)	-2.7 (5.9)	.093
POMS fatigue t-score	6.3 (9.2)	-.57 (9.8)	.024
POMS confusion t-score	-1.5 (12.2)	-1.1 (8.5)	.867

GW-deployed veterans with major depression showed significantly different mean change scores on five outcome measures compared with GW-deployed veterans without depression. On the cognitive/motor outcomes, performance improved. However, they reported more mood complaints at Time 2 on two POMS scales (depression and fatigue). These analyses were not run for the control group due to power considerations (PTSD, N=2; MDD, N=5).

KEY RESEARCH ACCOMPLISHMENTS

This study has repeated an in-depth neuropsychological, psychiatric and health-symptom evaluations of GW-era veterans at a second point in time (4 to 5 year time interval following initial evaluations), allowing longitudinal assessment of differences between GW-deployed and non-deployed veterans. Further, the study allowed a second chance at testing hypotheses arising from findings at the first testing interval (Time 1, 1995-98). To our knowledge, this is the first in-depth longitudinal assessment of GW veterans. The study also allowed an evaluation of *treatment seekers* using the same methods that had been used in a population study of a large group of GW veterans (Devens Cohort studies). Thus, comparisons of findings from these different types of groups are possible.

The assessments carried out during this study allowed detailed evaluation of a number of variables, including domain-specific neuropsychological functioning, health symptom complaints, chronic fatigue syndrome diagnosis, multiple chemical sensitivity diagnosis, post-traumatic stress disorder diagnosis and

major depressive disorder diagnosis. Finally, the results of this study have important implications for GW and deployment related health research and for treatment of GW-era veterans (see Conclusions).

REPORTABLE OUTCOMES

Abstracts:

1 Krengel, M., Sullivan, K., Proctor, S. P., & White, R. F. Neuropsychological deficits in treatment-seeking Persian Gulf War-era veterans, presented at the International Neuropsychological Society annual meeting in Denver, Colorado, February, 2000.

2. Sullivan, K., Krengel, M.,Ciota, M., Proctor, S. P., & White, R. F. Neuropsychological deficits in association with stress reaction and pyridostigmine bromide intake in Persian Gulf War-era veterans, presented at the International Neuropsychological Society annual meeting in Denver, Colorado, February, 2000.

3. Krengel, M., Sullivan, K., White, R., Honn, V., Proctor. Self-reported health symptoms of Gulf-war era veterans: How have they changed. Paper presented at the National Academy of Neuropsychology, October, 2002.

4. Sullivan, K., Krengel, M., White, R., Honn, V. Neuropsychological test performance in Gulf-war era veterans: Does Referral source matter? Paper presented at the National Academy of Neuropsychology, October, 2002.

5. Sullivan, K., Krengel, M., Honn, V., Proctor, S. P., & White, R. F. Neuropsychological functioning in Gulf War Veterans potentially exposed to chemical weapons at Khamisiyah, Iraq. Presented at the International Neuropsychological Society (INS) annual meeting in Hawaii, February, 2003.

6. White, R.F., Sullivan, K., Krengel, M., Proctor, S., Devine, S., Heeren, T., Vasterling, T. Effects of pyridostigmine bromide and PTSD on neuropsychological function in GW veterans. DAV Research Advisory Committee on Gulf War Veterans Illnesses. Washington, DC, June 16, 2003.

Published Manuscripts:

1. White, R.F., Proctor,S.P., Heeren, T., Wolfe, J., Krengel, M., Vasterling, J., Lindem, K., Heaton, K., Sutker, P., & Ozonoff, D., (2001) Neuropsychological function in Gulf War veterans: relationships to self-reported toxicant exposures. American Journal of Industrial Medicine, 40, 42-54.

2. White, R.F. (2003). Service in the Gulf War and Significant Health Problems: Focus on the Central Nervous System. Journal of Psychopathology and Behavioral Assessment, 25, 77-84.

3. Sullivan, K., Krengel, M., Proctor, S. P., Devine, S., Heeren, T., & White, R. F. (2003). Cognitive functioning in treatment-seeking Gulf War veterans: pyridostigmine bromide use and PTSD. Journal of Psychopathology and Behavioral Assessment, 25, 95-102.

4. Proctor, S.P., White, R.F., Heeren, T., Debes, F., Gloerfelt-Tarp, B., Appleyard, M., Ishoy, M., Guldoyer, B., Suadicani, P., Gyntelberg, F., & Ozonoff, D. (2003). Neuropsychological Functioning in Danish Gulf War Veterans. Journal of Psychopathology and Behavioral Assessment, 25, 85-94.

5. Lindem, K., Heeren, T., White, R.F., Proctor, S.P., Krengel, M., Vasterling, J., Sutker, P., Wolfe, J. & Keane, T. (2003). Neuropsychological Performance in Gulf War Era Veterans: Traumatic Stress Symptomatology and Exposure to Chemical-Biological Warfare Agents. Journal of Psychopathology and Behavioral Assessment, 25, 105-120.

6. Lindem, K., Heeren, T., White, R.F., Proctor, S.P., Krengel, M., Vasterling, J., Sutker, P., Wolfe, J. & Keane, T. (2003). Neuropsychological Performance in Gulf War Era Veterans: Neuropsychological Symptom Reporting. Journal of Psychopathology and Behavioral Assessment, 25, 105-120.

7. Lindem, K., Heeren, T., White, R.F., Proctor, S.P., Krengel, M., Vasterling, J., Sutker, P., Wolfe, J. & Keane, T. (2003). Neuropsychological Performance in Gulf War Era Veterans: Motivational Factors and Effort. Journal of Psychopathology and Behavioral Assessment, 25, 105-120.

8. Proctor, S.P., Harley, R., Wolfe, J., Heeren, T. & White, R.F. (2001). Health Related Quality of Life in Persian Gulf War Veterans. Military Medicine, Jun; 166 (6), 510-9.

9. Proctor, S.P., Heaton, K.J., White, R.F. & Wolfe, J. (2001). Chemical Sensitivity and Chronic Fatigue in Gulf War veterans: A Brief Report. Journal of Occupational and Environmental Medicine, Mar, 43 (3), 259-64.

Planned manuscripts:

1. Longitudinal assessment of neuropsychological functioning in Gulf War-Era Veterans.
2. Neuropsychological functioning in Gulf War veterans potentially exposed to chemical weapons at Khamisiyah, Iraq.

Funding:

1. A Cooperative Studies proposal (RF White, PI) was submitted to DVA based on some of these outcomes. The proposal was approved but not funded.

2. Drs. Krengel, Sullivan, Proctor and White submitted a grant application to the Department of Defense entitled " Neuropsychological functioning in Gulf War Veterans exposed to pesticide and pyridostigmine bromide" that was approved and funded as of February 1, 2004. This study will further evaluate toxicant exposures in a group of GW-deployed pesticide applicators and other military pest control personnel.

3. In June 2004, a Merit Review grant proposal was submitted to DVA (RF White, PI) based on some of these outcomes and focusing on MRI brain imaging with this sample of GW veterans. This grant is current under review.

7. CONCLUSIONS

Findings

Please note that all of these findings and conclusions are based on studies of *treatment-seeking* GW-era veterans, not population samples.

Neuropsychological test outcomes:

At Time 1 (1995-98), there were differences between the GW- deployed and non-deployed groups on neuropsychological test measures in three domains (motor, attention, short-term memory). When analyzing change scores over time (Time 2 – Time 1), it was found that significant differences were seen in the domains of motor control, visuoconstruction, and executive function.

Among the GW-deployed responders who were tested at both Time 1 and Time 2, scores showed significant declines in change scores on 2 out of 15 outcome measures (Digits Backward, Purdue Pegboard dominant hand) and improvement on a third (WMS Visual Reproductions delay). They also showed decreases in Tension and Vigor on the Profile of Mood States (POMS)(one improvement and one decline in mood on six measures). Among the non-deployed veterans, scores declined at statistically significant levels on three test outcomes (Purdue Pegboard, dominant and non-dominant hands; Block designs) and declined on POMS Vigor.

Summary conclusions:

The prior finding of differences between the deployed and non-deployed treatment seeking GW-era veterans in neuropsychological outcomes was not supported by the Time 2 mean change

score data. Also, the deployed veteran group did not perform worse at Time 2 than Time 1. This suggests that there was no progressive cognitive decline associated with GW deployment.

Exposure-test measure relationships:

Among GW-deployed veterans who self-reported exposure to pyrodistigmine bromide (PB), performance was better on a measure of visuoconstruction. Veterans with self-reported PB exposures complained of significantly more symptoms of angry at Time 2. Among GW-deployed veterans who self-reported exposure to pesticides, performance did not change significantly at Time 2. Among GW-deployed veterans who received notification that they had spent time near the Khamisyah weapons depot (with possible nerve gas agent exposure), performance was statistically worse than that of their non-notified counterparts on a measure of visual memory (one out of sixteen outcome measures) . No significant interaction effects were noted between the pesticide, PB or Khamisiyah groups.

Summary conclusions:

Self-reported exposure to PB and Khamisyah notification were related to only two outcome measures. Self-reported exposure to pesticides was not associated with changes in mood or cognitive symptoms over the four-year time period.

Health symptom complaints:

At Time 2, GW-deployed veterans reported significantly more aches and pains and joint pain than at Time 1. Controls also reported increased aches and pains, but to a lesser extent than the GW-deployed veterans. Additionally, the control group reported significantly less joint pain at Time 2.

Summary conclusions:

Treatment-seeking GW-deployed veterans reported increasing joint pain and aches and pains over a four year time interval, when compared with control veterans.

Post traumatic stress disorder:

Among GW-deployed veterans tested at both Times 1 and 2, the rate of PTSD increased slightly, from 16% to 21%. The increase is statistically non-significant, though rates at both evaluation periods were greater than those observed in the population-based Devens cohort. Among non-deployed veterans tested at both Times 1 and 2, the rate of PTSD was static at 10% of the group. At the current examination, among the GW-deployed veterans, PTSD diagnosis was not related to poorer test performance.

Summary conclusions:

Rates of PTSD may be higher in treatment-seeking groups. A few GW-deployed veterans may be converting over time from non-PTSD to PTSD diagnosis.

Major depressive disorder:

Among GW-deployed treatment seekers tested at both Times 1 and 2, the rate of diagnosis of MDD increased from 5% to 15% (did not reach statistical significance). Among non-deployed treatment seekers tested at both Times 1 and 2, the rate of diagnosis of MDD increased from 5% to 24% (did not reach statistical significance). Diagnosis of MDD in the GW-deployed group was related to increased mood complaints between time 1 and 2. Performance on measures of motor speed and mental tracking improved between Times 1 and 2 in the GW-deployed veterans with MDD.

Summary conclusions:

Rates of MDD increased somewhat in both groups. The question remains as to whether this increase is due to aging. It should be noted that these veterans did not report significant depression prior to military service and their cognitive abilities did not appear to decline with MDD diagnosis.

Chronic fatigue syndrome and multiple chemical sensitivity:

Less than 1% of the treatment seekers (regardless of GW deployment status) met criteria for CFS or MCS.

Summary conclusion:

Although MCS and CFS rates appear to be low in this population, health symptom complaints include fatigue.

Motivational issues:

Deployed veterans did not differ significantly from non-deployed veterans in effort to complete tasks, as measured by a test that is very simple and performed poorly by persons attempting to appear to be impaired.

Treatment and clinical implications

Among treatment seeking GW-era veterans, careful attention should be paid to possible PTSD or MDD symptoms. True cognitive declines in GW-deployed treatment seekers must receive special attention because they likely reflect some etiology other than deployment related exposures, PTSD, or MDD. Clinical care of GW-era veterans should focus on subjective feelings of ill- or well-health.

Treatment interventions such as cognitive behavioral therapy and exercise may benefit some veterans who feel ill. Other veterans will require psychotherapeutic and psychopharmacologic approaches to PTSD and MDD.

Research implications

It is essential to screen GW-era study participants for PTSD and MDD, which may affect study outcomes and which may also bias samples by over-inclusion of psychiatrically ill participants. Overall health perception is another important variable in GW research. Gender, education and age are important demographic control variables. More research could be done to address the possible adverse residual effects of pyridostigmine bromide exposure and exposure to the Khamisiyah weapons arsenal. Research addressing increased rates of MDD among GW-era veterans as they age may also be indicated. The results of this study, reflecting longitudinal in-depth evaluations of treatment-seeking GW-era veterans, suggest that similar longitudinal evaluations should be pursued in population-based samples.

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10. LIST OF PERSONNEL

PI: Roberta F. White, Ph.D., ABPP- no salary support
Co-Investigator, Clinical psychologist: Maxine Krengel, Ph.D.
Co-Investigator, Environmental Health Specialist: Susan P. Proctor- no salary support
Study Coordinator: Kimberly Sullivan, Ph.D.
Statistician: Timothy Heeren, Ph.D.
Post-doctoral Fellow: Vanessa Honn, Ph.D

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Annual meeting at San Francisco, CA August, 2001

A Re-examination of Neuropsychological Functioning in Gulf War-Era Veterans

Introduction:

Existing data from the Boston Environmental Hazard's Research Center suggest that Persian Gulf War (PGW) era veterans deployed to the Gulf have deficits on a limited, specific group of neuropsychological test measures as compared to PGW-era veterans who were not deployed to the Gulf. These findings raise the possibility of subtle, subclinical central nervous system damage associated with Gulf deployment and raise the question of whether such changes may be attributable to exposure to neurotoxicants in the Gulf environment. This latter possibility is particularly an issue because the existence of relative cognitive deficits was related in our sample to self-reported environmental exposures that are likely neurotoxic.

Recently some PGW veterans have reported that their cognitive functioning and mood complaints are worsening over the time since their return from the Gulf. Veterans are specifically reporting further deficits in the areas of short-term memory and attention. For instance, veterans report that they are having more difficulty remembering names and appointments and they are having difficulty completing work-related tasks. These reports are at odds with the usual course of central nervous system (CNS) effects of intoxication, which generally remit or remain static in the absence of exposure.

The specific aim of the project was to determine whether objective neuropsychological test measures reveal any progressive diminution in cognitive function among Gulf deployed PGW veterans by comparing test performance observed initially (1995-1998) with performance 4 years (+/- 6 months) later.

Subjects:

In our initial study, 207 PGW-deployed treatment seeking veterans were administered a thorough neuropsychological test battery including assessment measures from the domains of memory, attention and executive systems, visuospatial, language, motor and mood. Overall, neuropsychological deficits were found in the areas of attention and short-term memory when controlling for age, education and mood. Twenty-four individuals from our original GW deployed sample have been tested for a second time approximately four years after their first evaluation.

Preliminary Results:

Results of paired T-tests indicated similar performances on tests from most domains including attention and executive functions. The only significant finding was in the domain of nonverbal memory, specifically the WMS-R visual reproductions delayed recall. This performance improved significantly relative to the first testing.

Summary:

These preliminary results from our first 24 subjects suggest relatively static performances in GW veterans on test-retest measures with a four-year interval. These preliminary findings do not support continued diminution of veteran's performances on neuropsychological measures. However, neither do these performances suggest improvement of cognitive functioning over this time period. These results will be discussed as they relate to etiologic factors including possible neurotoxicant exposures. It is possible that this relatively static performance in our GW veterans could be consistent with long-term patterns expected from neurotoxicant exposure. However, continued follow-up of cognition and mood in these veterans should provide a clearer picture of this pattern.

Submitted for presentation at the American Psychological Association annual meeting in August, 2001, San Francisco, CA

A Re-assessment of current mood state in Persian Gulf War-Era Veterans

Introduction:

It has been found that Persian Gulf War (PGW) deployed veterans have reported a variety of mood complaints including depression, tension, anger and confusion since their return from the Gulf. These mood complaints have been reported to effect performance at work and have impacted social functioning, according to many PGW-deployed veterans. Some researchers have also found that these mood symptoms have had an effect on performance on a limited number of neuropsychological tests. Existing data from the Boston Environmental Hazard's Research Center suggests that PGW veterans deployed to the Gulf have significantly more mood complaints than their non-deployed counterparts. Although these complaints coexist with impairments in specific cognitive domains, we have found that neuropsychological deficits persist when controlling for current mood state. Given the impact of current mood on daily functioning, it is important to monitor mood state in PGW-deployed veterans in order to assist individuals in developing strategies to enhance social and occupational functioning.

We are currently following a clinical sample of over 200 PGW-era veterans, over half of whom were deployed to the Gulf during the war. Clinically, many of the PGW- era deployed veterans continue to report mood changes that have reportedly magnified over time since their return from the Gulf. Specifically, PGW-era deployed veterans report increased amounts of tension, depression and fatigue during clinical interview at a significantly higher rate than their non-deployed peers.

The specific aim of the current project was to determine whether mood measures revealed any progression of mood complaints among Gulf deployed PGW veterans by comparing scores observed initially (1995-1998) and those 4 years (+/- 6 months) later.

Subjects:

In our initial study, 207 PGW-deployed treatment seeking veterans were administered a thorough neuropsychological test battery including assessment measures from the domains of memory, attention and executive systems, visuospatial skills, language, motor speed and dexterity, and mood. PGW-era deployed veterans complained of fatigue, tension, depression, anger and confusion when compared to PGW-era nondeployed veterans. Twenty-four individuals from our original PGW-era deployed sample have returned to our clinic for follow-up. These individuals were interviewed and assessed for a second time approximately four years after their first evaluation.

Preliminary Results:

Results of paired T-tests indicated equal results for fatigue over four years in the deployed group, whereas levels of tension and anger diminished slightly relative to initial assessment. Confusion declined significantly from prior reports ($p = .05$). The only clinically significant mood complaint in this group of individuals is fatigue ($T = 58$).

Summary:

These preliminary results from our first 24 subjects suggest that current mood state has changed over time in PGW veterans on test-retest measures over a four-year interval. Specifically, mood complaints have become slightly less robust. These results will be discussed as they relate to follow-up neuropsychological test performance and social and occupational functioning in this group of PGW-deployed veterans.

Presented at the National Academy of Neuropsychology annual meeting. October, 2002.

disorder (RD) diagnostic groups. Results of the study indicated that profile analysis served to identify significant differences between ADHD and RD adult populations on Guilford's structure-of-intellect operation of memory, when applied to standardized assessment WAIS-R protocols. Conclusions support current research that adults diagnosed with reading disabilities will continue to experience academic difficulties on memory functions compared to ADHD individuals, particularly on symbolic memory measures, compromising their ability to effectively learn. The use of memory profile analysis may assist in identifying cognitive characteristics of RD and ADHD groups, and may also provide supportive information for more effective individualized academic planning and remediation in a college setting.

Neuropsychological test performance in Gulf War-era veterans: does referral source matter?
Sullivan K, Krengel M, Honn V, White RF

Gulf War (GW) veterans have reported a number of health symptoms since their return, including memory and concentration difficulties. These symptoms cause treatment providers to refer for objective neuropsychological testing. In this study we compared cognitive functioning in three groups of GW-era veterans to establish the appropriateness of clinical referrals and to establish whether subjective complaints were quantified using objective measures. One group of veterans was referred to our neuropsychology clinic specifically for cognitive concerns (CC) and one group was referred to other services besides neuropsychology (O). These two groups were compared with nondeployed veteran controls (ND). It was hypothesized that GW veterans who were specifically referred for neuropsychological complaints would show cognitive deficits consistent with those complaints, whereas, veterans referred to other services would show similar complaints but to a lesser degree. A one-way analysis of variance with three groups was conducted and results showed that the CC and O groups showed differences in the areas of complex tracking and set switching and spontaneous recall of verbal information. They also differed on the amount of vigor. They did not differ on a measure of response consistency. From these data, it appears that referrals for cognitive complaints were validated by objective measures in that individuals who reported cognitive concerns showed deficits on cognitive tests. However, it should also be noted, that GW veterans who do not necessarily complain of cognitive concerns, also exhibit deficits, albeit more mild, in these functional areas relative to nondeployed controls.

Neuroimaging correlates of Dementia Rating Scale performance at baseline and 12-month follow-up among patients with vascular dementia
Sweet LH, Paul RH, Browndyke JN, Cohen RA

We previously reported that subcortical hyperintensity (SH) and whole brain volume (WBV) each covary with different subscale scores of the Mattis Dementia Rating Scale (MDRS) among vascular dementia (VaD) patients. The present longitudinal analysis examined these relationships for change. We found that SH volume increased and WBV decreased significantly over 12 months. At baseline, SH volume accounted for the most variance in MDRS total score and attention, construction, and conceptualization subscale scores. WBV was unrelated to any MDRS measure. SH volume was unrelated to any MDRS score after 12 months, while WBV accounted for the majority of variance in attention and memory subscale performance, and a trend was evident for the MDRS total score. These findings indicate that while SH volume increases with disease progression, the relative impact of SH volume on cognitive status becomes less critical. Additionally, factors other than SH volume are important correlates of cognitive performance in patients with advanced VaD.

Presented at the National Academy of Neuropsychology annual meeting. October, 2002.

occupation could be resumed. Persistent verbal memory and visual impairments also limited vocational potential.

The influence of chemotherapy and radiation on neuropsychological test performance and self- reported functioning in breast cancer survivors

Jacquin K, Morse L, Adams-Price C, Ceminksy J, Wells-Parker E, Williams M

Cancer patients receiving chemotherapy or radiation treatment frequently report cognitive impairments (President's Cancer Panel, 1999). Five studies have examined the influence of chemotherapy on neuropsychological test performance in breast cancer patients (Ahles et al., 2002; Brezden et al., 2000; Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995). Although deficits were found, the effect sizes were fairly small (Jacquin et al., 2002). In addition, test deficits rarely matched self-report, suggesting that the tests do not tap everyday functioning or that some other factors account for the self-reported impairments. Our study examines this question by evaluating the performance of breast cancer survivors on ecologically valid neuropsychological tests. Participants ranged from 42 to 74 years of age ($M = 57.22$, S.D. $= 10.82$). The small sample size ($N = 18$) prohibited comparisons based on chemotherapy (83% had received it), but groups were compared on the basis of receipt of radiation (44%) and current hormonal therapy (44%). On the Rivermead Behavioural Memory Test, an ecologically valid measure of everyday memory problems (Wilson et al., 1989), 78% of our sample scored in the normal range, 11% showed mild impairment, and 11% scored in the moderately impaired range. However, there were not significant differences in test performance across treatment groups. Similarly, group differences were not found on the Everyday Cognition Battery (Allaire & Marsiske, 1999), Neuropsychological Symptom Inventory (Rattan et al., 1989; McCoy et al., 1998), or any other test. Complete results, implications, and suggestions for future research will be discussed.

Self-reported health symptoms of Gulf War-era veterans: how have they changed?

Krengel M, Sullivan K, White RF, Honn V, Proctor SP

In a sample of treatment seeking, GW-era veterans, our research has shown that the most common health symptoms 5 years after their return (Time I) included forgetfulness, headaches, fatigue, and joint pain. The aim of the current study was to determine if these same symptoms persist. Based on clinical observation of numerous GW veterans, it was hypothesized that veterans would continue to report the same symptoms and at a similar rate. Fifty treatment seeking Gulf War veterans were given a health symptom questionnaire 5 years after their return and again 4 years later as part of a larger longitudinal study of cognitive functioning in GW veterans. The health symptoms questionnaire included a checklist with 52 symptoms. Veterans were asked to rate on a scale from not at all (0) to very often, almost every day (4) as to how frequent each symptom was experienced. The 52 symptoms were grouped into major categories. The categories most frequently endorsed as being problematic at Time I were neuropsychological (cognitive memory and attention), psychological (depression, sleep disorder, anxiety), neurologic (headache, numbness, dizziness), musculoskeletal (joint pain, backache, neck ache), dermatologic (skin rash, eczema, skin allergies), and gastrointestinal (stomach cramps, nausea, diarrhea). Preliminary findings suggest that at Time II, veterans continued to report health concerns in the neurologic and neuropsychological categories at a rate consistent with Time I. Etiologic explanations for symptom complaints are discussed.

environmentally exposed to lead, and 30 individuals occupationally exposed to organic solvents were examined. Participants were administered a neuropsychological screening battery which included: Finger Tapping, Dynamometer, Grooved Pegboard, Santa Ana, Trail Making, Stroop, Symbol Digit Modalities, Rey-Osterrieth Complex Figure, WAIS–III Digit Span, Cancellation H, Consonant Trigrams, and Animal Naming. Seven participants were excluded for: scoring <7 on the Rey 15, history of alcohol abuse, insufficient vision, missing data, or a significant past head trauma. A one-way ANCOVA, between groups design, was used. The variables age, ethnicity, total years of exposure, and years of education were entered as covariates. Results revealed that the lead exposed individuals scored significantly lower on tests of psychomotor function (Finger Tapping, Dynamometer, Grooved Pegboard, and Santa Ana). This supports previous literature indicating psychomotor impairment as a primary symptom following lead exposure. The lead exposed group also had significantly lower test scores than the group exposed to organic solvents, on Trails A and B, Stroop color, Symbol Digit Modalities, Rey-Osterrieth Copy, and Digit Span reversed. Although attention, processing speed, cognitive flexibility, and visuospatial deficits are often cited after exposure to both lead and organic solvents, the present results may indicate different degrees of impairment based on type of exposure. Impairment levels within each group will be discussed.

Correspondence: *Melissa Hirt, Department of Psychology, San Francisco State University, 1600 Holloway Avenue, San Francisco, CA 94132. E-mail: missi333@hotmail.com*

K. SULLIVAN, M. KRENGEL, V. HONN, S. PROCTOR, & R.F. WHITE. Neuropsychological Functioning in Gulf War Veterans Potentially Exposed to Chemical Weapons at Khamisiyah, Iraq.

Gulf War (GW) veterans have reported several health symptoms since returning from the war, including memory and concentration difficulties. One hypothesis for these reported symptoms includes exposure to chemical or biological weapons (CBW). One documented chemical exposure of U.S. soldiers occurred in Khamisiyah, Iraq. This study assessed whether GW veterans notified of potential CBW exposure due to physical proximity to the Khamisiyah site (K) differed from GW veterans not exposed to the Khamisiyah site (NE). Most GW veterans were not aware of their exposure status during the time of this cognitive evaluation. It was hypothesized that GW veterans in the Khamisiyah group would show more cognitive impairment than GW veterans not exposed (NE). A multiple analysis of variance was performed and results showed that the K group showed significant differences in the areas of executive system functioning and fine motor control. They also differed on the amount of reported fatigue and confusion. From these data, it appears that GW veterans notified of potential CBW exposure from the Khamisiyah site performed worse than GW veterans not exposed to this site on measures of executive system functioning, mood and fine motor control. These cognitive domains are consistent with neurotoxicant exposure patterns that cause subtle changes in specific cognitive domains and not a generalized pattern of deficit.

Correspondence: *Kimberly Sullivan, Boston VA Medical Center, 150 S. Huntington Ave., 116B-4, Boston, MA 02130. E-mail: Sullivan.Kimberly@Boston.VA.gov*

L. O'FARRILL-SWAILS & M.L. ROHLING. The Neurotoxic Effects of Mercury Exposure: A Meta-Analysis.

This meta-analysis investigates the neurotoxic effects of mercury exposure. Previous research has examined 3 forms of mercury exposure: seafood consumption (e.g., longitudinal studies in the Seychelles and Faroes Islands), mercury vapor, and elemental mercury contained in amalgam tooth fillings. The study is designed to resolve differences in research methodology, types of exposure, and severity of impairment. To accomplish this, a comprehensive search of the literature was conducted. Results were analyzed to develop a dose–response relationship. Study inclusion criteria consisted of both pre- and postnatal exposure. Furthermore, studies were coded in terms of exposure type: food consumption, health-related (e.g., dental work), and occupationally related (e.g., miners). Studies were also coded by self-reported symptoms (sensory, pain, and psychological well-being) and objective performance (perceptual organization, attention, memory, verbal skills, executive functioning). This meta-analysis attempts to determine the magnitude of adverse neuropsychological effects, as well as the influence of exposure on emotional and personality functioning. The study also attempts to determine at what level the adverse effects of mercury exposure are statistically significant and clinically meaningful.

Correspondence: *Laura O'Farrill-Swails, 3458 Markham Drive, Mobile, AL 36609. E-mail: swails3@cs.com*

S. HUGHES, C. JORDAN, B. ROCHE, & E. SHAPIRO. Two-Factor Parent Model Predicts Developmental at 36 Months In At-Risk Children.

Maternal factors can mitigate the effects of poverty and associated environmental conditions or may increase the risk status of offspring. Previous work by the authors proposed a model of parental competence consisting of two empirically-derived factors: *Assets* (Raven Progressive Matrices, Home Observation Measure of the Environment, and Child Abuse Potential Inventory cognitive rigidity scale), and *Distress* (Global Symptom Index from the Brief Symptom Inventory, and Child Abuse Potential Inventory distress scale). Mothers of children in their second year of the DREAMS Child Development Study were divided into risk categories based on high/low dichotomization of these factor scores. A one-way ANOVA revealed significant group differences in child Mental Development Index (MDI) scores from the Bayley Scales of Infant Development at 36 months [$F(3,87) = 5.8, p = .001$]. *Post-hoc* analyses indicated that *high risk* mothers (Group 1: low assets, high distress) produced children with significantly lower MDI scores than *high competence* mothers (Group 4: high assets, low distress). Factor score configurations of *low asset/low distress* (Group 2) and *high assets/low distress* (Group 3) yielded intermediate MDI scores. These results support the validity of this 2-factor model of parent competence and the utility of categorization based on these factor configurations in predicting outcomes. Future research will focus on the utility of this model in predicting participation in longitudinal research. In addition, this model could serve to differentiate parents truly at risk from more competent parents living in high-risk communities.

Correspondence: *Steven J. Hughes, Ph.D., MMC 486 420 Delaware Street SE, Minneapolis, MN 55455. E-mail: hughe029@umn.edu*

C. JORDAN, S. HUGHES, & E. SHAPIRO. Maternal Risk Factors Predict Child Lead Burden.

Lead overburden is typically believed to be the result of poor housing conditions. It has been thought that maternal factors such as IQ and depression affect child development and their variance has been removed from that of developmental outcome in studies of lead sequelae. The relationship between maternal factors and risk of lead poisoning is not well understood but is relevant to understanding lead overburden as well as appropriate methods for controlling confounding variables in lead research. Previous work by the authors has proposed a model of parental competence consisting of the empirically-derived factors *Assets* (Raven Progressive Matrices, Home Observation Measure of the Environment, and the Cognitive Rigidity scale from the Child Abuse Potential Inventory, CAPI) and *Distress* (Brief Symptom Inventory Global Symptom Index and Distress score from the CAPI). The relationship between parental competence and risk for lead poisoning was examined in 76 mother–child pairs participating in the DREAMS Project, a prospective study of lead effects. Lead levels were collected every 4 months from 4 to 36 months and area under the curve computed. Cumulative child lead exposure at 36 months was compared between 4 maternal groups (*high asset/low distress*, *low asset/high distress*, etc.) using ANOVA ($F = 2.92$, $df = 3, 73$, $p < .05$). *Post-hoc* analyses documented a significant difference between Group 1 (low asset/high distress) and Group 4 (high asset/low distress). Maternal risk factors may help focus lead prevention strategies and need to be considered in decisions regarding treatment of confounding variables in lead research.

Correspondence: *Catherine Jordan, MMC 486, 420 Delaware St. SE, Minneapolis, MN 55455. E-mail: jorda003@umn.edu*

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Service in the Gulf War and Significant Health Problems: Focus on the Central Nervous System

Roberta F. White[1,2]

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The consensus of several studies on health among Gulf War (GW)-deployed veterans is that they have elevated symptom complaints. Central nervous system (CNS) symptoms among these veterans have been assessed in several investigations. Studies have disagreed as to whether there are neuropsychological deficits in GW-deployed veterans relative to controls. When differences between these groups have been found, they have often been attributed to stress or psychiatric factors, although exposures to neurotoxic substances present in the GW theatre have also been indicted as possible explanations. A review of the existing literature as well as the 5 papers contained in this issue of *Journal of Psychopathology and Behavioral Assessment* suggests that the neuropsychological and health symptom sequelae of GW zone service are multidetermined and cannot easily be explained on the basis of simplistic models of causation. Psychological, historical, and exposure parameters must be considered in the scientific evaluation of this problem.

KEY WORDS: Gulf War syndrome; stress; neurotoxicants; posttraumatic stress disorder; environmental exposures.

INTRODUCTION

Since the Gulf War (GW) ended in 1991 and substantial numbers of GW-deployed veterans began to report deterioration in health following return from war zone exposure, there has been considerable controversy concerning GW veterans' health and the possibility of a mysterious "Gulf War syndrome" associated with deployment to the Gulf during the war. This controversy has received widespread media coverage, a number of scientific meetings have been convened to discuss the issue, and several expert panels have been organized to summarize and critique the literature on this population. Because many of the prominent symptoms reported by GW-deployed veterans are behavioral and/or neurological, central nervous system (CNS) function in GW veterans has received a great deal of attention. From the outset, there has been disagreement among investigators as to whether the health complaints of these veterans reflect psychological factors such as "stress" or the physiological effects of GW theatre exposures to chemical or infectious agents.

This issue of the *Journal of Psychopathology and Behavioral Assessment* includes five research papers focusing on the issue of CNS function among veterans of the Gulf War. These papers summarize previously unpublished results of studies on neuropsychological function in a group of Danish GW veterans and in a group of treatment-seeking GW veterans from the United States, as well as three, in-depth analyses exploring the effects of stress, neuropsychological symptoms, and motivational factors on neuropsychological test performance in participants from a third study of GW veterans' health. These studies have been designed and/or directed by investigators from the VA Boston Healthcare System Medical Center (VABHS), where investigations of this population began in 1991, when veterans returned from the Gulf, and remain on-going. Researchers have focused on psychological health and stress, perceived health status, and the role of exposures to chemicals in the Gulf theatre on GW veteran health status. The present overview on the topic of CNS health in GW veterans briefly reviews and critiques

[1]Boston Environmental Hazards Center and Neuropsychology Service, VA Boston Healthcare System Medical Center, 150 South Huntington Avenue (116B-4), Boston, Massachusetts 02130; e-mail: rwhite@bu.edu.

[2]Departments of Neurology (Neuropsychology), Environmental Health, and Psychology, Boston University Schools of Medicine, Public Health, and Arts and Sciences, Boston, Massachusetts.

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existing research findings concerning health issues in this veteran population, summarizes the neuropsychological studies of GW veterans (including those contained in this volume), and discusses implications for future research.

Health Symptoms

Following the deployment of American military personnel to the Persian Gulf in 1990–91, a subgroup of GW-deployed veterans has reported that they have felt ill since returning from the conflict. About 15% of these veterans reported symptoms that could not be diagnosed (Kizer, 1995). Eleven years after the conflict and the initiation of studies on this population of deployed veterans, little definitive information has accrued on the *causes* of these health complaints. Several studies have documented that GW-deployed veterans have similar health complaints to those of varied control groups, including samples composed of military personnel deployed to other recent conflicts. However, GW-deployed veterans consistently report significantly *more* health complaints than control groups in studies of both American (Iowa Persian Gulf Study Group, 1997; Proctor et al., 1998) and foreign (Ishoy et al., 1999 [Danish]; Unwin et al., 1999 [UK]) troops. In addition, there have been recent reports in the media that service in the Gulf may be associated with increased risk for amyotropic lateral sclerosis (ALS) and that proximity to the Khamisiyah supply depot (which is known to have contained chemical warfare agents) at the time it was detonated by U.S. forces may be associated with higher mortality since the end of the war. All of these lines of evidence suggest that the health complaints of this veteran population deserve scientific scrutiny.

Several studies sampling individuals from the population of GW-deployed veterans have identified psychological and stress factors that appear to be associated with health complaints (Engel et al., 2000; Erickson, Wolfe, King, King, & Sharkansky, 2001; Lee, Gabriel, Bolton, Bale, & Jackson, 2002), but such variables have not provided a full, viable explanation of their reported health problems. This finding suggests that other factors have played a role in the appearance of health complaints. The identification of specific environmental exposures that may have triggered the experience of diminished health is critical but has been elusive. Some studies have identified self-reported exposures to chemicals known to have toxic (and especially neurotoxic) effects and that appear to be related to health symptom complaints and/or neurobehavioral deficits and neuroimaging findings (Haley et al., 1997, 2000; Proctor et al., 1998; White 2001). Candidate exposures of particular importance include smoke from oil well fires, exposure to chemical warfare agents, proximity to SCUDS, pesticides applied by local municipalities in the GW theatre and by US troops, vaccines received by the troops, and ingestion of pyridostigmine bromide (PB), a medication used to protect troops from chemical warfare agent exposure.

A particular problem in identifying critical exposure-outcome relationships in GW-deployed veterans is the fact that few data regarding exposures were collected at the time of the war. Records concerning which vaccines were received by each veteran, the number of PB tablets issued to individual veterans, and quartermaster records on pesticide supplies are lacking. Furthermore, very little data were collected on atmospheric contaminants present in the GW theatre. Therefore, there has been little reliable, objective exposure information that researchers have been able to use in systematic health studies. Thus, for researchers exploring exposure-outcome relationships, this line of work has been a little like searching for a needle in a very messy haystack, and investigators have been forced to rely on veterans' self-reports of theatre exposures. Further complicating the problem for scientists has been the fact that individual veterans likely were exposed to multiple potential toxicants, that there are almost certainly individual differences in susceptibility to these substances, and that the exposure-related health problems of GW veterans may vary among veterans (i.e., there is likely no single cause of GW veterans' health complaints).

Recently, attempts have been made to estimate objectively three different kinds of exposures that occurred in the GW environment. These have included the modeling of exposures to by-products of oil well fire smoke (Office of the Special Assistant for Gulf War Illnesses [OSAGWI], 1998; RAND, 1998), the identification of specific types of pesticide exposures in the Gulf (Fricker et al., 2000), and the modeling of an exposure plume resulting from detonation of the Khamisiyah supply depot containing chemical warfare agents. However, very few published studies have linked these sources of information to health or to objective measures of function in the large cohorts of GW veterans that have been followed since return from deployment. One recent study (McCauley, Lasarev, Sticker, Rischitelli, & Spencer, 2002) reported a possible increased cancer risk among GW veterans who were located within 50 km of Khamisiyah when compared to nondeployed controls. Although Khamisiyah-exposed troops reported more diagnoses of hypertension, PTSD, and depression, there was no increase in hospitalization rates.

The paucity of objective exposure-outcome data in GW-deployed troops is not surprising. The modeling of exposure, identification of locations in the war theatre

where high exposures likely occurred, and the linkage of these data to individual veterans or military units can take many years. For example, following the Vietnam War, the identification of Agent Orange exposure and the development of posttraumatic stress disorder (PTSD) as critical predictors of health problems among Vietnam veterans took many years following the deployment of troops to Vietnam, and full explication of the health effects themselves and the factors mediating these effects is still ongoing, over 30 years after the initial deployment of troops (cf. Brown et al., 2000). In the case of the GW, it was at least 5 years before systematic data were available even on the locations of the military units within the Gulf during deployment.

In addition to the problem of identifying the exposure-outcome relationships that may underlie GW-related health complaints, the studies published to date on GW-related health symptoms and illnesses have other significant shortcomings. In most cases, several years passed between return of troops from deployment and initiation of the study of their health complaints, resulting in potential recall bias for both symptoms and exposures. There are sparse longitudinal data on well-selected GW cohorts, there are problems with selection bias in the published cohort studies, and control groups have often been inadequate. Furthermore, the definition of "Gulf war-related illness" has been problematic and has ranged from individual health symptoms to case definitions of "Gulf War syndrome" to factor analysis-based "subsyndromes" of GW-related illness. The role of "stress" in GW-health problem reporting has been controversial, and definitions of stress and the treatment of "stress" as covariates or outcome measures in data analyses have varied widely and spawned debate. There has been a tendency in these investigations to rely on veteran self-report measures of health, with little or no verification of self-reported health problems through medical records or physical examinations. In addition, the prominence of certain symptoms such as fatigue or the self-report of constellations of multiple symptoms without a clear-cut diagnostic explanation has led to the use of syndromes or disorders such as multiple chemical sensitivity, chronic fatigue syndrome, or "chronic multisymptom illness" (CMI) as outcome measures. Use of these diagnoses has, in some cases, led to better compensation of GW veterans for their health problems (diagnosis of CMI is now compensable for GW veterans through VA disability benefits), but they have not clarified the etiology of health problems for these troops.

The methodological problems which have surfaced during research efforts have been important in helping investigators identify factors that must be considered when evaluating existing data on GW veterans and the data that must be collected in the future to control for confounders and "noise" when studying this group. Especially relevant candidate variables contributing "noise" to a research effort are some of the psychological factors discussed in the section below. However, these limitations in scientific study and other issues with the growing literature should not be used to conclude that there is no objective basis to the health complaints of GW veterans.

Central Nervous System Function

The major health symptom complaints reported by GW veterans soon after their return from deployment involved symptoms implicating the CNS. These included memory loss, concentration problems, headaches, and fatigue. For this reason, neuropsychological test methodology was applied relatively quickly to groups of GW veterans with such complaints. The application of this methodology was obvious and appropriate, because these measures provide an objective assessment of CNS function and are known to be capable of demonstrating subtle or preclinical effects of exposure to a variety of chemicals that are known to be neurotoxic (Anger, 1990; White, 2001; White, Feldman, & Travers, 1990; White & Proctor, 1992, 1997).

Rather early on, a few studies appeared in the literature that examined convenience groups of GW-deployed veterans. These studies varied in their findings, with some reporting deficits in these veterans compared to population norms (Axelrod & Milner, 1997) or controls (Hom, Haley, & Kurt, 1997). These early studies had many flaws, including selection bias, use of inappropriate controls, small sample sizes, and inadequate consideration of possible confounders. Some of the findings were suspect. For example, Hom et al. (1997) found differences between their target sample of GW-deployed veterans and controls on so many tasks that it is highly likely that the two populations had significant premorbid differences in cognitive function that were not adequately addressed in the data analysis (differences were seen on tests that are generally robust following exposure to neurotoxicants).

In addition to lacking control for premorbid intellectual capacities, the need to control for psychopathology was demonstrated in at least three other relatively early studies. Goldstein, Beers, Morrow, Shemansky, and Steinhauer (1996) found that differences in neuropsychological test performance observed between a GW-deployed veteran sample and an occupational clinic-based control group disappeared when psychopathology was included as a variable in data analysis. Similarly, when data from another study (Axelrod & Milner, 1997)

were reanalyzed considering "emotional factors" such as depression and stress, the apparent cognitive deficits disappeared (Sillanpaa, Agar, Milner, Podany, Axelrod, & Brown, 1997). Vasterling, Brailey, Constans, Borges, and Sutker (1997) also reported that GW-deployed veterans in their sample who were diagnosed with posttraumatic stress disorder (PTSD) appeared to have lower premorbid intelligence than those who were not diagnosed with PTSD. Other potential confounders that did not receive adequate attention in some of the early studies included demographic variables, motivational factors, health status, and substance abuse issues.

Beginning in the mid-1990s, several large cohort studies funded by the Department of Veterans Affairs, Department of Defense, Centers for Disease Control and Prevention, and other sources were initiated to examine neuropsychological function in GW veterans, with careful consideration of potential confounders. A group of investigators in Portland, OR, carried out such work on a large sample of GW-deployed veterans who were assigned to "case" or "control" groups using broad criteria for the diagnosis of "GW illness" case status. In their studies, cases were found to show mental slowing relative to controls (Anger et al., 1999; Storzbach et al., 2000; Storzbach, Rohlman, Anger, Binder, & Campbell, 2001). These investigators reported a weak association between self-reported cognitive symptoms and objective neuropsychological test findings (Binder et al., 1999), an association that was also observed by researchers at the Boston study site (Lindem, 2000; Lindem et al., 2003). On the basis of their studies and those of others, the Portland researchers concluded that there is heterogeneity among GW veterans. They therefore examined a subgroup of veterans who met diagnostic criteria for chronic fatigue syndrome (CFS), finding that GW-deployed veterans with CFS showed lower premorbid cognitive abilities (as measured by Armed Forces Qualification Test results obtained at the time of entry into the Service) but that this subgroup also performed more poorly than controls on some neurobehavioral tests even when controlling for these premorbid differences (Binder, Storzbach, Campbell, Rohlman, & Anger, 2001). No conclusions were reached concerning whether GW service itself or some exposure occurring during such service was related to the development of CFS in their population sample. In contrast, Proctor, Heaton, White, and Wolfe (2001) found that the rate of diagnosable CFS was low in the Devens cohort, a group of about 3000 GW-deployed veterans who have been studied since their return from the war. A recent study examined olfactory function in GW-deployed veterans as a potential measure of neurotoxicant-related CNS dysfunction in GW veterans (Vasterling, Brailey, Tomlin, Rice, & Sutker, 2003). When comparing performance on olfactory tests among 72 GW-deployed veterans and 33 military personnel activated during the GW but not deployed to the GW zone, no differences in olfaction were observed. Given the toxicants that were reportedly present in the Gulf theatre and that were addressed by this study, the lack of positive findings is not surprising.

Research efforts conducted by White et al. (2001) using both Devens cohort members and a sample of treatment seekers who were deployed to the Gulf showed subtle CNS dysfunction in these groups. Although stress symptomatology and motivational factors were identified as important potential confounders, not all of the findings using neuropsychological test measures could be explained on the basis of these factors alone. Among Devens cohort members, self-reported exposure to pesticides was found to be predictive of mood complaints several years after deployment, and self-reported chemical warfare exposure was related to several measures of cognitive dysfunction (White et al., 2001). These results were robust despite extensive control for confounders. Interestingly, studies on a sample of *treatment-seeking* GW-deployed veterans did not reveal the same exposure-outcome relationships. Rather, in this group, self-reported exposure to pyridostigmine bromide and diagnosis of PTSD were predictive of poorer neuropsychological test performance relative to controls (Krengel et al., 1999; Sullivan et al., 2001, 2003; White, 1999).

This aggregate of research findings suggests that both health problems and relative dysfunction on cognitive tests are related to factors such as "stress" or "distress," but that no available measures of these entities provide a full explanation of the available data (Binder et al., 1999; Proctor et al., 1998; Storzbach et al., 2000; White et al., 2001). Similarly, the presence of PTSD as a war-related disorder does not account for findings, although as indicated, mental disorders and symptoms may be shown to influence results. The prevalence of PTSD has not been identified at especially high rates in GW veteran samples (Ismail et al., 2002; Wolfe, Brown, & Kelley, 1993; Wolfe, Erickson, Sharkansky, King, & King, 1999). For example, a current PTSD prevalence of 12.5% was observed among 775 Louisiana-based Persian Gulf war zone veterans (Sutker, Davis, Uddo, & Ditta, 1995), and PTSD was found in 10.9% of a subset of 348 of these troops reassessed an average of 13 months following initial evaluation (Benotsch, Brailey, Vasterling, Uddo, Constans, & Sutker, 2000). These results can be compared to current and lifetime PTSD prevalence rates of 15% and 31% in community-based samples of Vietnam combat veterans (National Vietnam Veterans Readjustment Study (NVVRS); Kulka et al., 1990).

Two critical issues are highlighted by the accumulating literature on neuropsychological function in GW veterans. One of these involves affective status. Because the limbic system and neurotransmitters are particularly vulnerable to the effects of toxicant exposures, long-lasting symptoms of dysphoria are sometimes seen in persons exposed to such substances (White, 2001; White, Feldman, & Proctor, 1992; White & Proctor, 1997). Therefore, it is important to consider the issue of dysphoria in evaluating the effects of chemical exposures. If the decision is made to measure and control for a psychological variable such as "depression" or "dysphoria" in data analyses, it is possible to overcontrol for—and therefore obscure—the very outcome of interest (i.e., brain damage attributable to exposure). Another issue is that of clinical versus "subclinical" presentations of CNS dysfunction. Neuropsychologists often comment that if they look at the neuropsychological test protocols of GW veterans, they do not observe patterns in individual clinical data that would suggest an encephalopathy or a neuropsychological syndrome. However, this diagnostic approach is inappropriate in epidemiological studies, where dose-effect relationships on specific neuropsychological tasks or within certain behavioral domains may be uncovered in individuals who appear to be "within normal limits" on diagnostic examinations or in clinician–patient interactions. Data from Boston Environmental Hazards Center investigators on GW-deployed veterans and groups of research participants with well-defined occupational exposures support these dissociations (Baker et al., 1984; White et al., 2001; White, Proctor, Echeverria, Schweikert, & Feldman, 1995; White, Robins, Proctor, Echeverria, & Rocksay, 1994).

In summary, careful neuropsychological studies of rather large cohorts of GW veterans conducted in Boston and in Portland have suggested that there are several potential confounding variables that must be evaluated carefully in research of this type. These include premorbid intelligence, existence of developmental disorders of learning or attention, psychiatric disorders and psychopathology traced to pre- and postdeployment time frames, stress symptomatology assessed as a continuous variable, as well as diagnosed PTSD, motivational factors evaluated by including tasks that assess effort to perform well (and quantified on a continuous or ordinal basis rather than simply a dichotomous decision of malingering/not malingering), disability application status, and severity of self-perceived ill health. With the exception of the research conducted in Boston, there has been almost no investigation of exposure-outcome relationships in the neuropsychological literature on GW veterans, and this work to date has relied on self-reported exposures.

CONCLUSION

Investigations published to date on both health and neuropsychological functions have confirmed the importance of controlling for confounder variables as well as establishment of clear definitions for outcome measures and toxicant exposures. More work is needed to explore *objective* measures of exposure to environmental contaminants, through modeled exposures, unit locations in the Gulf, and other proxy indicators of likely exposure. Use of functional imaging and other confirmatory approaches to the neuropsychological findings would bolster their evidentiary strength. Longitudinal studies to determine whether neuropsychological dysfunction persists in individuals from the population of Gulf War zone exposed veterans would be of considerable interest. Despite limitations inherent in retrospective work, the carefully controlled studies evaluating health symptoms and using objective measures of neuropsychological function that have been completed to date have reached the same conclusion: psychological factors appear to contribute to the dysfunction seen in GW-deployed veterans, but they do not comprise a complete and adequate explanation of the outcomes observed. There can be little doubt that the work summarized in this series of papers barely scratches the surface in unraveling the complex factors that influence neuropsycholobiological outcomes to war zone duty in environments characterized by multiple hazards. However, the research investigations described in this collected series are important in their comprehensiveness in examining the impact of GW service on the neuropsychological function, health, and overall subjective well-being of GW-exposed troops.

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Cognitive Functioning in Treatment-Seeking Gulf War Veterans: Pyridostigmine Bromide Use and PTSD

Kimberly Sullivan,[1,2,3,5] Maxine Krengel,[1,2,3] Susan P. Proctor,[2,3] Sherral Devine,[1] Timothy Heeren,[4] and Roberta F. White[1,2,3]

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Gulf War (GW) deployed veterans have reported health symptoms since returning from the war that suggest dysfunction of the central nervous system (CNS). These symptoms include memory and concentration difficulties, fatigue, and headaches. Leading hypotheses for the etiology of these cognitive complaints include psychological factors and/or exposures to chemicals with neurotoxic properties. In this study, cognitive functioning was compared in treatment-seeking GW-deployed veterans and a treatment-seeking non–GW-deployed veteran control group. Results indicated that GW-deployed veterans performed significantly worse than the comparison group on tests of attention, visuospatial skills, visual memory, and mood. GW-deployed veterans who reported taking pyridostigmine bromide (PB) performed worse than GW-deployed veterans without PB use on executive system tasks. Treatment-seeking GW-deployed veterans with diagnoses of posttraumatic stress disorder (PTSD) did not differ on cognitive test measures compared with GW-deployed veterans without PTSD. No interaction effect of PTSD and PB use was found.

KEY WORDS: Gulf War syndrome; environmental toxicants; posttraumatic stress disorder; neuropsychological testing.

Gulf War (GW) veterans have reported a constellation of health symptoms since returning from the theatre that have been referred to collectively in the popular media as the "Gulf War syndrome." These symptoms include memory and concentration difficulties, joint pain, fatigue, and headaches (Proctor et al., 1998). Suggested causes of these symptoms include exposure to environmental toxicants such as diesel fuel, pesticides, pyridostigmine bromide (PB) pills, and biological or chemical warfare agents (Abou-Donia, Wilmar, Jensen, Oehme, & Kurt, 1996; Haley & Kurt, 1997). Other researchers have suggested that sequelae from psychological stress reactions including posttraumatic stress disorder (PTSD) may contribute to the picture of cognitive symptoms reported by "sick" GW veterans (Goldstein, Beers, Morrow, Shemansky, & Steinhauer, 1996; Sillanpaa et al., 1997, Vasterling, Brailey, Constans, Borges, & Sutker, 1998).

Studies assessing the relationship between environmental exposures and cognitive functioning in veterans deployed to the Gulf theatre (Proctor et al., 1998) have been forced to rely on self-report of exposures. Military records are incomplete, and it is impossible to document objectively most of the toxicant exposures that may have occurred in the Gulf theatre during the war. In addition, veterans often do not know which chemicals were present in the war environment or which exposures they may have experienced. It is likely, however, that GW-deployed veterans can recall with reasonable accuracy whether they used the anti–nerve gas agent PB, because the pills were self-administered (Proctor et al., 1998). This study, therefore, focused on the relationship between self-reported exposures to PB and objectively measured cognitive functioning.

[1]Department of Neurology, Boston University School of Medicine, Boston, Massachusetts.
[2]Department of Environmental Health, Boston University School of Public Health, Boston, Massachusetts.
[3]Boston Environmental Hazards Center, Boston VA Healthcare System Medical Center, Boston, Massachusetts.
[4]Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston, Massachusetts.
[5]To whom correspondence should be addressed at Boston VA Healthcare System Medical Center, 150 South Huntington Avenue 116B-4, Boston, Massachusetts 02130; e-mail: Sullivan.Kimberly@boston.va.gov.

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Pyridostigmine bromide is an acetylcholinesterase (ACh) inhibitor used by U.S. military personnel during the GW as a prophylactic treatment against chemical weapon attack. Its mode of action involves the reversible binding of acetylcholine receptors in the peripheral nervous system to serve as a protector against chemical weapon exposures (e.g., soman and sarin) that irreversibly bind to ACh receptors. The drug generally does not cross the blood–brain barrier or have centrally acting effects. Evidence from animal models (Friedman et al., 1996; Van Haaren et al., 2001) suggests that PB intake combined with acute stress reactions may have a synergistic effect on the CNS, affecting the permeability of the blood brain barrier and allowing PB to have a central effect. According to this theory, PB disrupts normal CNS functions, causing confusion, fatigue, and cognitive difficulties (Moss, 2001; Van Haaren et al., 2001).

Psychological stress reactions are also a suspected contributor to the cognitive and health complaints of GW-deployed veterans (Sillanpaa et al., 1996; Vasterling et al., 1998). In fact, the hypothetical relationship between physical health symptoms and psychological stressors in GW-deployed veterans has raised several important questions regarding illness mechanisms. For instance, it has been found that stress reactions, characterized by physiological arousal and anxiety, are associated with reports of deteriorating health status, including cognitive declines in memory, concentration, and attention (e.g. Shalev, Bleich, & Ursano, 1990; Wolfe, Kelley, Buscela, & Mark, 1992). Other researchers have suggested that prolonged stress can lead to long-term hormonal changes (Yehuda, 1997), reduced immune system functioning (Black, 1994), and alterations of neurotransmitters that mediate cognitive and psychological responses (Wolfe & Charney, 1991). Severe and prolonged stress reactions, such as PTSD, may be associated with chronic physiological arousal that becomes particularly severe when the affected individuals are exposed to triggers similar to the original traumatic event (Charney, Deutch, Krystal, Southwick, & Davis, 1993). Exposure to stressful and traumatic events has also been shown to be associated with cognitive impairment, including decreased attention on tracking tests (Sutker, Vasterling, Braile, & Allain, 1995; Vasterling et al., 1998) and increased health symptom reporting (Engel, Liu, McCarthy, Miller, & Ursano, 2000).

In the present study, treatment-seeking veterans were targeted specifically to evaluate the possibility of CNS dysfunction associated with exposures experienced in the GW environment by examining veterans who spent time in the Gulf and who considered themselves to be "sick" or in need of treatment. These veterans seemed to be the most likely to show war zone service associated CNS dysfunction, if any could be detected. Additionally, a non–GW-deployed treatment-seeking veteran group that was on military duty during the Gulf era was included in study design to control for the variable of treatment-seeking (i.e., considering oneself to be sick or possibly sick). Neuropsychological performances were examined in veterans with exposures to PB and those with PTSD diagnosis.

METHODS

Participants

All treatment-seeking veterans from the VA Boston Healthcare System (VABHS; i.e. those seeking treatment for any condition) who were in the military during the time of the GW (1990–91) were considered to be potential study participants. Two recruitment sources were targeted. The first group of participants came from a random sampling of GW-era veterans who were seeking treatment or diagnostic evaluation for any type of health or adjustment complaint at any of the greater Boston VA health clinics. Study participants that comprised the GW-deployed group were recruited from a random listing of 400 treatment-seeking GW-era veterans. From this list, a total of 87 GW-deployed veterans agreed to participate in the study protocol. An additional 53 treatment-seeking non–GW-deployed veterans were recruited from the random listing of GW-era veterans, and they comprised the control group. The second recruitment source included consecutive referrals of GW-deployed veterans who were referred specifically for neuropsychological evaluation at the VABHS because of cognitive or health symptom complaints ($n = 120$). In order to increase statistical power for the analyses, a decision was made to combine the two GW-deployed groups. To assess the appropriateness of combining the groups, a comparison of the participants' reported health symptoms was performed. Results suggested similar frequency and type of complaints between the two groups of GW-deployed veterans. These symptoms included memory and concentration difficulties, headaches, mood disorder, joint pains, and fatigue. Combining the two GW-deployed groups, there were 207 GW-deployed participants and 53 non–GW-deployed GW-era treatment-seeking veterans.

The study was approved by the VABHS Institutional Review Board. The first contact with potential study participants was by telephone (or by mail, if there was no telephone number available). The initial contact consisted of a description of the project, including types of assessment, time required, and financial reimbursement for study participation. Veterans consenting to participate were screened to determine whether they met preliminary

study inclusion criteria. Inclusion criteria were treatment-seeking status for any reason, enlistment in the military during the time of the Gulf War (1990–91), and age range between 20 and 55 years. Exclusion criteria were current treatment for alcohol or other substance abuse, sensory or motor impairments precluding use of the computer, and a history of serious brain injury prior to the GW. Prior substance abuse and current medications were recorded but did not constitute exclusion criteria for this study. Two participants were excluded from the study because of alcohol intoxication. Informed consent was obtained from each of the remaining 260 study participants.

Protocol and Measures

The study protocol included an environmental exposure interview, a clinical interview, psychological assessment measures (questionnaire and structured clinical interviews), and a neuropsychological test battery. The study questionnaire was used to ascertain self-reported exposures to PB, pesticides, debris from SCUDs, and smoke from burning oil well fires. Exposure to PB was treated as a dichotomous variable (yes/no). PTSD diagnosis was determined by structured clinical interviews including the Clinician-Administered PTSD Scale (CAPS-DX; Blake et al., 1995) using *Diagnostic and Statistical Manual of Mental Disorders, Third Edition—Revised* (*DSM-III-R*) criteria (American Psychiatric Association [APA], 1987). Current cognitive functioning was determined by neuropsychological evaluation.

The psychological interviews and semistructured clinical interview were administered by a clinical psychologist, who is one of the coauthors (MK). They included the Structured Clinical Interview for *DSM-IV* (SCID; Spitzer, Williams, Cribbon, & First, 1990), the Clinician-Administered PTSD scale (CAPS-DX; Blake et al, 1995) and a semi-structured clinical interview. The SCID is used to determine Axis I psychiatric disorders and has been shown to be reliable (Wolfe & Keane, 1993). The CAPS-DX is a state-of-the-art instrument for confirming the diagnosis of current or lifetime PTSD (or both), as well as for evaluating the intensity, frequency, and severity of the disorder and its individual symptom criteria. The semi-structured clinical interview elicited information pertaining to current or past mood disorders, substance abuse, neurological and medical illness, traumatic brain injury, history of other traumatic events, birth trauma, developmental delays, and history of learning disability. Diagnosis of PTSD was determined by the CAPS-DX using *DSM-III-R* criteria. PTSD diagnosis was entered into analyses as a dichotomous yes/no variable. Only current and war-related PTSD diagnoses were used in the analyses.

Table I. Neuropsychological Test Battery

General intellectual abilities
Information Subtest (WAIS-R, Wechsler, 1981)
Attention and executive function
Digit Span Subtests (WAIS-R; WMS-R, Wechsler, 1987)
Trail-Making Test (Reitan & Wolfson, 1985)
Continuous Performance Test (Visual CPT, NES2; Letz, 1988)
Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977)
Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993)
Stroop Test (Golden, 1978)
Motor/psychomotor abilities
Finger Tapping (Reitan & Davidson, 1974)
Purdue Pegboard Test (Purdue Research Foundation, 1948)
Visuospatial constructional abilites
WAIS-R Block Design
Hooper Visual Organization Test (HVOT; Hooper, 1958)
Memory
Paired Associate Learning—WMS-R
Visual Reproductions—WMS (Wechsler, 1945)
California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987)
Mood and Malingering
Profile of Mood States (POMS; McNair et al., 1971)
Test of Memory Malingering (TOMM; Tombaugh, 1996)

The neuropsychological test battery (see Table I) was administered by trained staff who were blind to participant exposures or health-related information. The protocol was selected from a more extensive battery that has been employed in prior work with research participants who were being assessed for brain damage from environmental or occupational exposure to neurotoxicants (White & Proctor, 1992). All of the tests have reliable psychometric properties and have been widely used for both research and clinical purposes. The tests were drawn from two major categories: (1) tests tapping relatively stable premorbid cognitive/intellectual abilities, and (2) tests that have been shown to have high specificity and sensitivity for detecting changes in localized or diffuse cognitive brain functions. Tests in the first category provided uniform estimates of baseline abilities for all individuals. The more specialized tests assessed functions that may be differentially affected by a particular disease or condition (Lezak, 1995).

Data Analyses

Multivariate analyses of covariance (MANCOVA) were used to compare the performance between treatment-seeking GW-deployed veterans and the non–GW-deployed comparison group on each of the neuropsychological test outcomes. The GW-deployed group was

significantly older than the control group and included significantly less women than the control group. Therefore, multivariate analyses were performed adjusting for age and sex. To control for multiple comparisons, the neuropsychological test outcomes were grouped by domain, and MANCOVAs were performed to test for overall effects by domain between the GW-deployed and non–GW-deployed control groups. The Wilks' lambda value and its associated p value were used to examine the significance of the multivariate analysis testing.

MANCOVA was also used in a second analysis consisting only of GW-deployed veterans to assess main effects of PB exposure, PTSD diagnosis, and the interaction effect of PB exposure and PTSD diagnosis. For all analyses, an alpha level of .05 was considered to be significant.

RESULTS

Description of Participant Groups

Comparisons of mean age, education, and sex representation of the GW-deployed and control groups showed significant differences between groups for age and sex representation (see Table II). No significant differences in educational attainment were found between the GW-deployed (13.4 years) and comparison groups (13.9 years). Of the 207 GW-deployed study participants, 92 (84 men and 8 women) endorsed using PB pills (44%). Mean age and education levels were not significantly different between participants with and without PB use when compared by Student's t tests (age $t = .05$, $p = .96$; education $t = .49$, $p = .62$), and sex differences were not found between the groups when compared by Pearson's Chi-square test ($\chi^2 = .04$, $p = .84$).

A total of 28 study participants met criteria for PTSD (13.5%), including 21 men and 7 women. Study participants with and without PTSD diagnoses were not statistically different in mean age or educational level when compared by student's t tests (age $t = .66$, $p = .51$; education $t = .59$, $p = .56$). However, Pearson's chi-square test was significant for sex differences, indicating a higher proportion of women in the group with a PTSD diagnosis ($\chi^2 = 7.6$, $p = .006$).

Table II. Participant demographics

	Mean (*SD*)		
	GW-deployed ($n = 207$)	Non–GW-deployed ($n = 53$)	Signif. of Group Diff.
Age	35.6 (8.7)	30.8 (10.3)	.003
Education in years	13.4 (1.9)	13.9 (1.8)	.20
WAIS-R Information, age-scaled score	9.9 (.19)	9.9 (.41)	.82
Sex (percent female)	8.5%	20.4%	.02

Comparisons on Neuropsychological Test Outcomes

Results for the multivariate and univariate analyses are presented in Table III. To control for multiple comparisons and the large number of analyses performed, the significance of the findings was evaluated in a two-step process: first, examination of the domain-specific MANCOVA p value ($p < .05$) and then of the univariate test-specific p value ($p < .05$). All analyses were adjusted for age and sex unless otherwise specified. The GW-deployed veterans performed significantly worse than the non–GW-deployed veterans on tests in the functional domains of attention (WAIS-R Digit Span), visuospatial skills (WAIS-R Block Design) and visual memory (Visual Reproductions delay, Rey–Osterreith delay). Mood was also significantly different between the groups: every scale from the Profile of Mood States (POMS) was higher in the GW-deployed group, with the exception of the Vigor scale (see Table III). Performance on a test of motivation (TOMM) was also significantly lower in the GW-deployed group. Therefore, analyses were rerun removing data from participants with TOMM scores below 45. The results did not change significantly (WAIS-R Digit Spans forward $p = .04$; Trail Making A $p = .04$; WAIS-R Block Designs $p = .001$; Visual Reproductions delay $p = .003$; Rey–Osterreith delay $p = .004$).

Comparisons of GW-Deployed Veterans with PTSD and Reported Neurotoxicant Exposures

To assess the impact of PTSD diagnosis and PB exposures on cognitive functioning in GW-deployed veterans, an analysis was performed for the separate and then combined impact of PTSD and PB exposure in a 2×2 MANCOVA model. GW-deployed veterans with a diagnosis of PTSD scored significantly higher on the mean Tension, 52.6 (8.7) versus 43.8 (8.4) respectively, and Depression, 50.3 (9.2) versus 43.9 (8.4) respectively, scales of the POMS compared with their non-PTSD counterparts. However, no other significant differences were found on any neuropsychological measures (see Table IV). GW-deployed veterans reporting PB use showed significant differences on the WCST mean number of sorts, 3.5 (1.7) versus 3.9 (.78) respectively. No significant effects were observed for the PB-Exposed × PTSD interaction,

Table III. Comparisons of GW-Deployed and Non–GW-Deployed Veterans on Selected Neuropsychological Measures, Controlling for Age and Sex

		Mean (*SD*)		
	MANCOVA *p* value	GW-deployed ($n = 207$)	Non–GW-deployed ($n = 53$)	Univariate *p* value
Attention	.002**			
WAIS-R Digit Span, Forward Span		6.6 (.01)	7.2 (.18)	.008**
WAIS-R Digit Span, Backward Span		5.1 (.11)	5.4 (.22)	.008**
Trail-Making A (time)		31.9 (.84)	26.9 (1.33)	.06
Executive system	.12			
WCST, # of sorts		3.4 (.01)	3.7 (.16)	.54
Stroop—Words		90.0 (1.6)	96.2 (2.3)	.09
Stroop—Colors		67.3 (1.3)	74.1 (1.8)	.004
Stroop—Word/Color		38.6 (.87)	45.2 (1.34)	.001
PASAT Trial 1–4, # correct		114.1 (9.0)	128.8 (1.4)	.08
Trail-Making B (time)		77.7 (2.8)	63.9 (4.4)	.29
Motor and visuomotor	.003**			
Finger Tapping, dominant		49.5 (.68)	50.5 (1.3)	.31
Finger Tapping, nondominant		44.9 (.63)	45.7 (1.1)	.63
WAIS-R Block Design, age-scaled score		10.3 (.17)	11.6 (.35)	.01**
Verbal memory	.17			
WMS-R Verbal PAL, immediate		16.9 (.11)	18.6 (.16)	.35
WMS-R Verbal PAL, delay		6.9 (.00)	7.5 (.00)	.10
CVLT, Trial 1–5, # correct		53 (.15)	58 (.32)	.04
CVLT, SDFR, # correct		10.2 (.23)	11.7 (.38)	.08
CVLT, SDCR, # correct		11.3 (.22)	12.5 (.38)	.05
CVLT, LDFR, # correct		10.4 (.26)	11.9 (.38)	.02
CVLT, LDCR, # correct		11.3 (.24)	12.3 (.41)	.07
CVLT, Recogn., # correct		13.9 (.17)	14.7 (.32)	.002
Visual memory	.003**			
WMS Visual Reproduction, immediate		10.6 (.20)	11.6 (.29)	.19
WMS Visual Reproduction, delay		9.0 (.25)	10.9 (.41)	.007**
Rey-O Copy, raw		33.8 (.31)	33.4 (.69)	.32
Rey-O Immediate, raw		21.3 (.52)	23.9 (.98)	.07
Rey-O Delay, raw		20.8 (.50)	24.3 (.86)	.009**
Mood and motivation	.001**			
POMS Tension (*t*)		45.5 (.67)	40.7 (1.24)	.001**
POMS Depression (*t*)		45.1 (.64)	41.6 (1.19)	.02*
POMS Anger (*t*)		50.4 (.73)	46.4 (1.04)	.01**
POMS Vigor (*t*)		52.2 (.69)	57.1 (1.40)	.001**
POMS Fatigue (*t*)		54.2 (.67)	47.2 (1.13)	.001**
POMS Confusion (*t*)		49.1 (.67)	41.8 (1.05)	.001**
TOMM Trial 1, # correct		47.3 (.30)	48.9 (.23)	.02*

*$p \leq 0.05$. **$p \leq 0.01$.

suggesting that veterans who reported both PB exposure and PTSD did not differ from veterans who reported PB exposure alone, PTSD alone, or neither PB exposure nor PTSD (Table IV).

DISCUSSION

In this study, possible CNS dysfunction associated with the GW environment was evaluated by assessing GW-deployed veterans who considered themselves to be sick or in need of treatment. The GW-deployed group included individuals specifically referred for neuropsychological evaluation because of cognitive complaints. Also included was a non–GW-deployed GW-era treatment-seeking comparison group to control for effects related to being a treatment seeker. When comparing treatment-seeking GW-deployed veterans to treatment-seeking non–GW-deployed veterans, differences were seen on tests of attention, visuospatial skills, and visual memory

Table IV. Comparisons of PB Exposure and PTSD Diagnosis Subgroups of GW-Deployed Veterans on Selected Neuropsychological Measures

	PB exposure[a]		No PB exposure[a]				
Domain/measure	PTSD ($n = 17$)	No PTSD ($n = 75$)	PTSD ($n = 11$)	No PTSD ($n = 36$)	p value$_{PB}$	p value$_{PTSD}$	p value$_{PB \times PTSD}$
Attention					.14	.55	.52
WAIS-R Digit Span, Forward Span	8.8 (2.5)	8.5 (2.0)	6.7 (2.1)	7.9 (2.1)	.18	.34	.33
WAIS-R Digit Span, Backward Span	7.0 (2.7)	6.9 (2.3)	5.7 (3.8)	7.4 (2.3)	.41	.25	.27
Trail-Making A (time)	32.5 (10.2)	31.2 (11.3)	28.3 (10.2)	29.7 (9.8)	.71	.68	.58
Executive system					.01*	.92	.91
WCST, # of sorts	3.5 (1.7)	3.5 (1.2)	4.8 (.50)	3.9 (.78)	.01*	.49	.40
Stroop—Words	84.7 (30.1)	92.0 (15.1)	76.0 (25.4)	90.5 (12.8)	.68	.84	.75
Stroop—Colors	65.3 (20.1)	65.9 (13.8)	64.5 (13.4)	71.7 (9.5)	.19	.88	.98
Stroop—Word/Color	41.0 (14.5)	39.2 (9.4)	37.5 (5.0)	39.1 (6.7)	.43	.84	.73
PASAT Trial 1–4, # correct	124.1 (33.8)	121.2 (32.7)	107.0 (22.0)	123.3 (26.7)	.32	.76	.60
Trail-Making B (time)	77.6 (26.1)	73.9 (33.1)	72.8 (24.3)	67.2 (26.9)	.34	.50	.55
Motor and visuomotor					.89	.72	.82
Finger Tapping, dominant	48.3 (10.4)	51.0 (7.9)	44.5 (20.6)	51.2 (8.0)	.91	.40	.52
Finger Tapping, nondominant	43.7 (8.7)	45.8 (7.8)	40.4 (13.8)	47.0 (8.7)	.54	.47	.61
WAIS-R Block Design, age-scaled score	31.7 (11.3)	10.4 (2.5)	10.8 (2.6)	31.9 (7.9)	.89	.30	.44
Verbal memory					.12	.19	.29
WMS-R Verbal PAL, immediate	16.8 (3.9)	17.4 (3.8)	17.3 (3.8)	17.4 (3.9)	.14	.69	.60
WMS-R Verbal PAL, delay	6.8 (1.5)	7.0 (1.3)	7.8 (.50)	7.4 (1.1)	.52	.80	.60
CVLT, Trial 1–5, # correct	49.3 (9.0)	50.8 (9.7)	55.0 (13.1)	55.8 (8.6)	.01	.97	.85
CVLT, SDFR, # correct	10.7 (2.9)	10.0 (3.0)	12.5 (1.7)	11.7 (2.4)	.004	.85	.89
CVLT, SDCR, # correct	11.1 (3.1)	11.3 (2.8)	13.0 (2.6)	13.0 (1.9)	.003	.53	.70
CVLT, LDFR, # correct	9.5 (3.1)	10.6 (3.4)	13.0 (3.8)	12.2 (2.9)	.01	.90	.80
CVLT, LDCR, # correct	10.6 (3.6)	11.4 (2.9)	12.0 (4.1)	12.7 (2.7)	.03	.25	.51
CVLT, Recogn., # correct	14.3 (1.6)	14.1 (2.0)	12.3 (4.7)	14.7 (2.0)	.20	.06	.06
Visual memory					.38	.55	.55
WMS Visual Reproduction, immediate	10.8 (2.3)	10.8 (2.6)	12.3 (.58)	11.2 (2.5)	.37	.59	.38
WMS Visual Reproduction, delay	9.6 (2.4)	9.0 (3.6)	10.7 (1.2)	10.5 (2.9)	.07	.74	.93
Rey-O Immediate, raw	21.7 (5.5)	21.5 (5.8)	23.0 (2.8)	22.5 (5.6)	.26	.98	.94
Rey-O Delay, raw	21.6 (5.4)	21.2 (5.8)	24.8 (.35)	22.5 (5.6)	.18	.68	.80
Mood and motivation					.09	.05*	.17
POMS Tension (t)	51.8 (8.6)	42.5 (8.0)	58.3 (6.2)	43.3 (8.8)	.10	.006**	.46
POMS Depression (t)	49.2 (8.3)	42.6 (7.8)	55.3 (7.6)	44.3 (8.7)	.38	.04*	.61
POMS Anger (t)	53.5 (8.0)	47.7 (9.1)	57.8 (6.9)	49.3 (10.2)	.65	.15	.72
POMS Vigor (t)	50.1 (9.4)	52.3 (8.7)	47.3 (12.7)	54.8 (9.7)	.91	.37	.95
POMS Fatigue (t)	57.7 (10.2)	51.9 (9.4)	60.5 (7.9)	55.3 (10.2)	.03	.50	.61
POMS Confusion (t)	54.9 (9.3)	46.2 (9.2)	53.0 (10.6)	48.3 (7.8)	.20	.75	.20
TOMM Trial 1, # correct	45.0 (6.2)	48.1 (2.2)	49.7 (.58)	48.7 (1.9)	.46	.55	.04

[a]Values are mean and standard deviation, with the latter in parentheses.
*$p \leq 0.05$. **$p \leq 0.01$.

measures, with GW-deployed veterans scoring more poorly than non–GW-deployed veterans. Mood scale measures (POMS) were also significantly elevated in every category in the GW-deployed group. Results remained significant when study participants with questionable TOMM scores were eliminated from the analyses. Taken together, these results suggest that treatment-seeking GW-deployed veterans are experiencing more dysfunction than non–GW-deployed treatment-seeking GW-era veterans and are not simply expressing "typical" treatment-seeking cognitive performances but rather showing lower performances on objective tasks assessing specific cognitive domains. Results support findings of deficits in response speed and efficient set switching ability in a subgroup of GW-deployed veterans (Lange et al., 2001) and are in contrast with those reported by Hom, Haley, and Kurt (1997), who suggested that GW-deployed veterans displayed generalized deficits rather than domain-specific effects.

The POMS results are consistent with previous reports of increased mood complaints in GW-deployed veterans, and some investigators have concluded that mild decrements in cognitive testing performance among GW-deployed veterans can be explained on a psychogenic basis (Goldstein et al., 1996; Sillanpaa et al., 1997). However, a population-based study of GW-deployed veterans in the Northwest (Anger et al., 1999) concluded that emotional factors contribute to subjective complaints in these populations but do not explain the behavioral test results in a subgroup of GW-deployed veterans. Another report (Lange et al., 2001) confirmed that post-war psychiatric diagnoses contributed to cognitive performances when evaluating GW-deployed veterans but did not account for all of the findings. Other research has documented that significant differences in performance on tests assessing specific cognitive domains remained unchanged after controlling for depression symptomatology (POMS Depression scale) and motivational factors (TOMM; White et al., 2001). These findings indicate that dysphoria did not explain the differences seen in performance on cognitive tasks seen in the present study. In addition, mood changes often accompany documented neurotoxicant exposures that are associated with significant cognitive deficits (Baker et al., 1984).

To evaluate the impact of severe stress (PTSD) and PB exposures on cognitive functioning in GW-deployed veterans, analyses were performed to assess the separate and combined impact of PTSD and PB exposure. Results showed that PTSD diagnosis was associated with elevated scores on the POMS mood scales but not with lower performance on cognitive tasks. However, self-reported PB use was found to be associated with decrements in performance in executive system functioning. Poor performances on tests assessing executive system functioning have been related to a number of different types of toxicant exposures (White et al., 2001; White & Proctor, 1992).

Hypotheses suggesting synergistic effects of extreme stress reactions (defined as PTSD diagnosis) and exposure to PB (Friedman et al., 1996; Van Haaren et al., 2001) were not confirmed in this study. PB exposure was associated with significantly lower scores on one test assessing executive system functioning, although this pattern was not found when comparing PB in combination with PTSD diagnosis. It should be noted, however, that the sample sizes were small and significant findings may not have emerged because statistical power was insufficient to detect them in the PB × PTSD group. The finding that participants with and without PTSD performed similarly on cognitive testing is inconsistent with some prior literature on GW-deployed veterans (Vasterling, Root, Brailey, Uddo, & Sutker, 1993).

Perhaps the most important limitation in this study was the restricted nature of the exposure assessments. Determination of PB exposure was made using veteran self-reports, which was the only possible method given the lack of independent records on PB use in the GW theatre. Whether the participants' beliefs about PB exposure and potential effects of PB adversely affected their neuropsychological performance is unknown. This appeared unlikely because each study participant was asked to complete a lengthy questionnaire reporting any toxicant exposure during his or her lifetime as well as specific exposures during the GW. The study participants were not told which exposures would be analyzed. Therefore, motivational factors related to PB exposure or PTSD diagnosis should not have affected the results in any systematic way. In addition, the examiners performing the neuropsychological evaluations were blind to the exposure status of the veterans. Whether study participants reporting PB usage were more likely to be exposed to other neurotoxicants is also not known. However, study participants reporting PB usage did not endorse higher numbers of toxicant exposures on their questionnaires than veterans not endorsing PB use. Finally, other analyses comparing self-reported exposures to pesticides and burning diesel fuels were not found to be significantly associated with performance on the neuropsychological battery in these treatment-seeking veterans.

Studies reporting neuropsychological functioning in GW-deployed veterans have predominantly reported poorer neuropsychological function on tasks assessing attention and memory (Anger et al., 1999; Goldstein et al., 1996; Hom et al., 1997; Sillanpaa et al., 1997; White et al., 2001). However, these studies have proposed differing etiologies for the cognitive findings, ranging from emotional effects (Sillanpaa et al., 1997) to toxicant-induced encephalopathy (Hom et al., 1997). Although it appears that emotional factors contribute to cognitive functioning in GW-deployed veterans, they do not appear to explain all the reported cognitive deficits in this group (White et al., 2001). Clinically diagnosable toxicant-induced encephalopathy has not been documented in GW-deployed veterans, but subclinical deficits as a result of chemical exposures remain a possibility (White & Proctor, 1992), given the current finding of deficits in the cognitive domains of attention, visuospatial skills, and visual memory. These three domains are often sensitive to CNS effects of neurotoxicant exposures in documented cases of subclinical encephalopathy (White & Proctor, 1992). It appears from these studies and similar findings that there is a continued need for follow-up of GW-deployed veterans who feel that they are "sick" or in need of treatment to explore the etiology of cognitive deficits. Current findings

support the need for additional research on the effects of PB and other chemical exposures in order to assess why GW-deployed veterans continue to show cognitive and health complaints 10 years following their military service. However, caution should be exercised with regard to implications of the limited significant findings related to PB exposure in this group of GW-deployed veterans. Whether these findings are generalizable to other groups of GW veterans remains to be seen. Examination of a larger sample of exposed veterans might help to elucidate any causal relationships between cognitive decrements and PB exposure combined with extreme stress conditions. When approaching the study of GW-deployed veterans, innovative methods of exposure assessment and confirmatory measures of brain function for the neuropsychological test results (e.g. functional imaging techniques) may be informative in obtaining a clearer picture of health patterns in these veterans.

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Neuropsychological Functioning in Danish Gulf War Veterans

Susan P. Proctor,[1,2,3,4] Roberta F. White,[1,2,4] Timothy Heeren,[4] Frodi Debes,[5] Birte Gloerfelt-Tarp,[5] Merete Appleyard,[5] Torben Ishoy,[5] Bernadette Guldager,[5] Poul Suadicani,[5] Finn Gyntelberg,[5] and David M. Ozonoff[4]

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Research has shown that Danish Gulf War (GW) veterans reported a significantly higher prevalence of neuropsychological symptoms than did military controls 6 years after GW deployment. To explore the possible central nervous system determinants of these complaints, neuropsychological tests were administered to stratified, random samples of the Danish cohort of 916 GW-deployed veterans and 236 non–GW-deployed participants. Multivariate analyses of covariance were used to analyze neuropsychological test outcomes among the 215 male participants (143 GW-deployed and 72 non–GW-deployed soldiers). No significant differences in neuropsychological test performances were found between the GW-deployed and non–GW-deployed groups. Troops deployed to the GW reported significantly more mood complaints (i.e., fatigue and confusion) than their nondeployed counterparts. Because they were assigned to the Gulf region during the postcombat phase, Danish GW soldiers differed from the majority of American GW-deployed troops in military assignments and possible toxicant exposures.

KEY WORDS: Gulf War veterans; cognitive function; environmental exposures.

Six years after deployment, Danish Gulf War (GW) veterans reported a significantly higher prevalence of neuropsychological symptoms than did non–GW-deployed controls. These symptoms included concentration or memory problems, repeated headaches, balance disturbances or fits of dizziness, abnormal fatigue not caused by physical activity, and problems sleeping all night (Suadicani, Ishoy, Guldager, Appleyard, & Gyntelberg, 1999). Because of the high prevalence of neuropsychological symptoms, the central nervous system (CNS) function of stratified random samples of Danish GW-deployed veterans and non–GW-deployed military personnel was investigated further using neuropsychological testing techniques.

Previous studies examining the neuropsychological functioning of GW-deployed veterans have varied in their study design and in their findings, with some investigators reporting deficits compared to population norms (Axelrod & Milner, 1997) or controls (Hom, Haley, & Kurt, 1997) and other studies identifying subsets of poorer performers within the GW-deployed group (Anger et al., 1999; Storzbach et al., 2000; Storzbach, Rohlman, Anger, Binder, & Campbell, 2001). Investigation of a group of American GW-deployed veterans compared to a group of Germany-deployed GW-era veterans found evidence of significant differences in mood complaints. Also, subtle differences in neuropsychological functioning in the domains of attention, executive function, and memory, as well as adverse mood states, were linked to Gulf theatre–related environmental exposures (White et al., 2001).

Approximately 95% of the Danish military personnel deployed to the Gulf region in 1991 were involved in peacekeeping and cleanup operations after the war had ended. Thus, they differ from most American GW-deployed soldiers in that they were not deployed for nor did

[1]Boston Environmental Hazards Center, VA Boston Healthcare System, Boston, Massachusetts.
[2]Boston University School of Medicine, Boston, Massachusetts.
[3]National Center for PTSD, VA Boston Healthcare System, Boston, Massachusetts.
[4]Boston University School of Public Health, Boston, Massachusetts.
[5]Bispebjerg Hospital, Copenhagen, Denmark.
[6]To whom correspondence should be addressed at Boston Environmental Hazards Center, VA Boston Healthcare System Medical Center (116B-4), 150 South Huntington Avenue, Boston, Massachusetts 02130; e-mail: sproctor@bu.edu.

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they participate in direct combat activity. Also, because of the timing of their deployment (generally post–February 1991) and their mission, Danish GW-deployed soldiers experienced somewhat different environmental exposures than most American GW veterans. For example, only a small percentage of Danish soldiers reported ingestion of antinerve gas pills or having been within 2 km of SCUD missile explosions (Ishoy et al., 1999).

The present study examined whether Danish GW-deployed veterans performed differently from non–GW-deployed military personnel on neuropsychological tests. The study was also conducted to describe relationships between neuropsychological test performance and self-reported exposure to specific Gulf theatre neurotoxicants by comparing the Danish GW-deployed veterans who reported each exposure to those who did not report each exposure. In summary, the present work (1) explored whether Danish GW-deployed veterans showed evidence of CNS dysfunction on neuropsychological tests, particularly involving attention and memory, compared to non–GW-deployed military controls; and (2) examined whether performance on neuropsychological tests was related to self-reported chemical exposures experienced in the Gulf.

METHODS

Between January 1997 and January 1998, Danish investigators conducted a cross-sectional clinical examination study of Danish GW-deployed veterans and a group of randomly selected Danish military personnel who were not deployed to the Gulf region (Ishoy et al., 1999). A total of 686 GW-deployed soldiers (83.6% of the total number of Danish GW-deployed forces) and 231 military personnel controls (representing 57.7% of the Danish Armed Forces at that time who were not deployed to the Gulf) participated. The study protocol for the 1997–98 investigation included a comprehensive questionnaire developed in collaboration with the Boston Environmental Hazards Center (Drs White, Proctor, and Ozonoff; Proctor et al., 1998) and a clinical medical examination that incorporated standard laboratory tests and interviews with a physician. Diagnoses were assigned using the World Health Organization (WHO) International Classification of Diseases, Revision 10 (ICD-10; WHO, 1992). A diagnosis of post-traumatic stress disorder (PTSD; yes/no) was made by Danish clinicians in accordance with the ICD-10 criteria. The Regional Ethical Review Committee for Copenhagen and Frederiksberg (Denmark) approved the protocol in 1997, and informed consent was obtained from the 917 study participants.

Participants

For the follow-up neuropsychological study, GW-deployed and control military personnel were selected using a stratified, random sampling strategy. The strategy was designed to insure that the distribution of higher and lower health symptom reporters in the sample reflected that of the larger cohort. This was done in order to minimize the potential for participation bias in this follow-up study (i.e., reduce the occurrence of either the most ill veterans or the least ill veterans returning for the follow-up). This sampling strategy was the same used to select a sample for a neuropsychological study of American GW-deployed veterans involving Devens Cohort Study members (White et al., 2001). Containing only participant identification numbers, the sampling list was developed in Boston and forwarded to the Danish investigators, who conducted the recruitment, tracking, and testing of military personnel. Thus, the Danish research team was blind to categorization of "higher or lower" symptom status during all phases of recruitment, testing, and interviewing.

A total of 225 individuals from the targeted sample participated (75% of the intended sample of 300). Seven were women, and gender information was missing for three veterans. For the data analysis, the sample was reduced to 215 male participants (143 GW-deployed and 72 control participants) because the number of women was not sufficient to evaluate gender effects. The Institutional Review Boards at the Centers for Disease Control and Prevention, Boston University, and Bispebjerg Hospital in Copenhagen, Denmark, approved the protocol and procedures for the study. Additionally, approval from the U.S. Office for Protection from Research Risks (OPRR) was required, because the study involved international collaboration; OPRR approved the protocol and procedures in February 1999. The present study examined subsets of the Danish GW-deployed veterans and control military personnel between February 1999 and December 1999, with the majority of individuals being tested before May 1999.

Sampling

Self-reported health symptomatology collected in the Danish study questionnaire during the initial study in 1997–98 was used to perform the sampling. The 20-item Health Symptom Checklist (Bartone, Ursano, Wright, & Ingraham, 1989), in which each participant was asked to report the frequency that he/she experienced symptoms over the past several weeks, was used. Any response higher than "not at all" was considered endorsement of

a symptom for sampling purposes, similar to the strategy applied in selecting a subset of Devens Cohort Study GW-deployed veterans for follow-up study (Proctor et al., 1998). In the initial Danish GW-era study conducted in 1997–98, the median number of symptoms reported by the 686 Danish GW-deployed veterans was 2.0 ($SE = 0.11$) and 1.0 ($SE = 0.13$) for the 231 control military personnel.

Categorization of the GW-deployed soldiers into higher- and lower-symptom individuals for the purpose of selecting a stratified, random sample to assess neuropsychological functioning was established by splitting the group using the median number of health symptoms reported in 1997–98. Those participants reporting >2 symptoms were classified as higher symptom reporters, while those reporting ≤2 symptoms were classified as lower symptom reporters. Also, when conducting the sampling procedure, further categorization of the higher symptom reporters into two distinct groups was performed to allow comparisons with another cohort study of GW-deployed veterans, in which the median number of health symptoms was 5.0 (Proctor et al., 1998). Thus, those Danish GW-deployed veterans reporting greater than two but less than or equal to five symptoms were categorized further as "moderate" and those reporting greater than five symptoms were categorized as "high" symptom reporters. To select the subset of control group soldiers for targeted follow-up, a simple random sample was derived.

Neuropsychological Test Battery

The battery of neuropsychological tests administered (see Table I) was designed by one of the coauthors (RW) and was comparable to the battery administered to a subset of GW-deployed veterans from the Devens Cohort Study and comparison group of Germany-deployed GW-era veterans (White et al., 2001) and other studies of GW-era veterans (Sullivan et al., 2003). The Danish version of the Wechsler Adult Intelligence Scale—Revised (WAIS-R) Information subscale (Wechsler, 1981) and the Test of Memory Malingering (TOMM; Tombaugh, 1996) were included in the test battery to serve as control measures for the assessment of premorbid intelligence and effortful test performance, respectively. The other tests were included as possible indicators of CNS dysfunction.

Environmental Exposures

Questionnaires designed to identify subjects' GW-service experiences and exposures were administered to the larger cohort during the initial study (Ishoy et al., 1999). These instruments were not readministered as part of this follow-up study assessment. Thus, data from the initial study questionnaire were used to determine self-reports of environmental exposures in the GW-deployed group. The questions encompassed a list of over 50 different GW-service hazardous exposures. A subset of approximately 18 of these exposures (e.g., exposure to diesel, kerosene, and other fumes; insecticides against cockroaches, etc.) was noted to be significantly associated with neuropsychological symptomatology in analyses of the larger cohort (Suadicani et al., 1999).

Data Analyses

Univariate comparisons of demographic variables and individual symptom rates of the Danish GW-deployed veterans and control military personnel were conducted using Student's t tests for continuous variables or chi-square statistics for categorical variables. Preliminary analyses showed that the stratified sampling procedure resulted in samples that represented the distribution of

Table I. Neuropsychological Test Battery

Domain tested	Neuropsychological test	Outcome measures
Basic academic knowledge	WAIS-R Information subscale (Wechsler, 1981)	Raw score
Attention, executive function, working memory	Continuous Performance Test (Letz, 1990)	Mean response time
	Trail-making Test (Halstead, 1947)	Time to completion
	Wisconsin Card Sorting Test (Grant & Berg, 1948)	Number
Motor skills	Purdue Pegboard (Purdue Research Foundation, 1948)	Time to completion
Visuospatial abilities	WAIS-R Block Designs (Wechsler, 1981)	Raw score
Verbal memory	California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987)	Raw scores
Visual memory	WMS Visual Reproductions (Wechsler & Stone, 1945)	Raw scores
Mood, affect	Profile of Mood States (McNair, Lorr, & Droppleman, 1971)	Raw scores
Motivation	Test of Memory Malingering (Tombaugh, 1996)	Raw score

reported symptoms in the larger cohorts. Since there was no evidence of participation bias based on symptom reporting, weighting or adjusting for the number of reported symptoms was deemed unnecessary. Multivariate analyses of covariance (MANCOVA) were used to compare the GW-deployed and control groups for each of the neuropsychological test outcomes. The GW-deployed group was significantly older than the control group, and therefore multivariate analyses were performed adjusting for age unless otherwise specified. To control for multiple comparisons, the neuropsychological test outcomes were grouped by domain (see Table I), and MANCOVAs were performed to test for overall effects by domain between the GW-deployed and non–GW-deployed control groups. The Wilk's lambda value and associated p value were used to examine the significance of the multivariate analysis testing. Follow-up analyses comparing the graded test performances across the non–GW-deployed group and the low, medium, and high symptom GW-deployed groups were performed only if both the domain-specific and the test-specific analyses demonstrated significant differences between the overall GW-deployed and the non–GW-deployed groups.

MANCOVAs (similar to the procedure described above) were used to compare neuropsychological test performance differences between Danish GW-deployed personnel reporting exposure to specific hazardous agents while in the Gulf theatre and those without each exposure. The environmental exposures examined included those known to be neurotoxicants with effects on the CNS, those found to be associated with diminished neuropsychological functioning in other research studies of GW-deployed veterans, and those for which an adequate sample was available. Reported exposure to depleted uranium, bathing in or drinking contaminated water, and contact with dead animals were also examined because these exposures were identified by Suadicani et al. (1999) as being significantly related to increased neuropsychological symptoms in the Danish cohort. For all analyses, an alpha level of .05 was used.

RESULTS

Descriptive characteristics of the Danish GW-deployed veteran and control groups were compared using unweighted analyses (see Table II). No significant differences between the groups were observed except that the control group was significantly younger than the GW-deployed group and more likely to report being in excellent or very good health. Of the cases of PTSD in the GW-deployed group, four of the seven were attributed to a GW service–related event, while three of the cases were not. The frequency of GW-related environmental exposures reported by this group of Danish GW-deployed soldiers is presented in Table III.

Table II. Descriptive Characteristics of Danish GW-Deployed and Non–GW-Deployed Groups

Variable	GW-deployed ($n = 143$)	Non–GW-deployed ($n = 72$)
Age, years [$M(SD)$]	38.8 (9.7)	34.8** (9.0)
WAIS-R information, raw score [$M(SD)$]	21.5 (3.7)	21.6 (3.7)
TOMM score[$M(SD)$]	48.9 (1.5)	49.1 (1.0)
PTSD diagnosis (%)	4.9	2.8
Married (%)	71.8	71.8
Current smokers (%)	38.7	39.4
Current health rating: Excellent or very good (%)	78.0	92.9**

Note. TOMM = Test of Memory Malingering; PTSD = Posttraumatic Stress Disorder.
*$p \leq .05$. **$p \leq .01$.

To examine possible participation bias (i.e., more ill persons would be more or less likely to participate in study procedure), qualitative comparisons between the rates of individual symptoms reported by the initial Danish cohort (reported by Ishoy et al., 1999) and the rates reported by members of the follow-up group at the time of the initial study were made. Findings indicate that the subsets of participating GW-deployed and comparison subjects were generally representative of the larger cohorts from which they were selected in terms of symptomatology (see Table IV). This was particularly true with regards to the five neuropsychological symptoms that had been identified as significant in prior studies (see Suadicani et al., 1999).

Results for the multivariate and univariate analyses of neuropsychological test performances, comparing the GW-deployed and non–GW-deployed groups, are presented in Table V. To control for multiple comparisons and the large number of analyses performed, the significance of the findings was evaluated in a two-step process: first, examination of the domain-specific MANCOVA p value ($p < .05$) and then of the univariate test-specific model p value ($p < .05$). The Danish GW-deployed group reported significantly more mood complaints, particularly higher levels of Fatigue and Confusion on the Profile of Mood States (POMS), compared to the non–GW-deployed controls. Although results for individual tests within the neuropsychological domains of executive function and verbal memory were suggestive of

Table III. Physical, Chemical, and Biological Exposures Related to Persian Gulf Service Reported by GW-Deployed Soldiers Who Completed Neuropsychological Testing

Exposure	Frequency in GW-deployed group (%)
Sand or dust storms	83.1
Ingestion of local food	76.8
Insect bites	68.1
Diesel, kerosene, or other fumes	61.0
Being inside destroyed Iraqi tanks	60.6
Bathing in or drinking local water	54.2
Skin contact with diesel or other petrochemical fuel	53.9
Burning of waste or manure	47.9
Oil well fires	45.1
Engaged in cleaning work	40.1
Worked on planes or at airport	33.1
Contact with dead animals	30.3
Evaporated diesel oil used on the ground to prevent dust and sand drift	27.9
Other paints and solvents	24.8
Lotions or spray against fleas, insects	24.6
Confronted with dead bodies	24.6
Insecticides against cockroaches	20.4
Direct combat activities	19.7
Bathing in or drinking contaminated water (fumes, oil, chemicals)	12.8
Gave aid to victims of war	12.0
Ingestion of contaminated food (by fumes, oil, chemicals)	9.9
POW exposure	9.9
Gave first aid to victims	8.5
Tooth brushing using water contaminated with chemicals or pesticides	5.6
Radar	5.0
Heard alarms or put on protective gear	4.9
Depleted uranium	2.8
CARC paint	2.1
Scud missiles hit within 2 km	1.4
Mustard gas or nerve gas	0.7
Mammal, animal bites	0.7
Biological warfare agents	0
Scorpion bites	0
Experienced sexual assault or rape, harassment	0

Note. Exposures are sorted in descending order of prevalence. A total of 2.6% reported receiving anthrax vaccine (23.7% indicated they did not know) and a total of 2.3% reported ingesting antinerve gas pills (3.3% indicated they did not know).

poorer test performances by the GW-deployed group compared to the non–GW-deployed group, overall domain-specific differences in performances were not statistically significant. Significant differences for the POMS Fatigue and Confusion Scales were observed when comparing the non–GW-deployed group mean scores to the medium- and high-symptom GW-deployed group mean scores, with higher scores (i.e., more complaints) in the medium- and high-symptom GW-deployed groups than in the non–GW-deployed group (see Table VI). Also, significant differences were observed when comparing the GW-deployed group with a low number of symptoms to that with medium numbers of symptoms and when comparing the low-symptom group to the high-symptom group on the POMS Fatigue and Confusion Scales. The difference between the medium- and high-symptom groups on the POMS Confusion Scale was also significantly different, but not on the Fatigue Scale ($p = .06$).

Following the two-step MANCOVA procedures described above, no significant differences on neuropsychological test performances were noted between those reporting exposure (compared to those reporting no exposure) to spray/lotions for insect repellents; insecticides for cockroaches; diesel fuel, kerosene, or other fumes; evaporated diesel fuel on the sand; oil fire smoke; exposures resulting from being engaged in cleaning work; direct

Table IV. Neuropsychological Symptoms Reported by GW-Deployed and Non–GW-Deployed Groups

Diseases or symptoms reported during the preceding 12 months with onset during or after the Gulf War/August 1990	Rates Reported by Larger Danish Study Cohort			Rates Reported by Subset of Cohort that Underwent Neuropsychological Testing		
	GW-deployed ($n = 686$) %	Non–GW-deployed ($n = 231$) %	p value	GW-deployed ($n = 143$) %	Non–GW-deployed ($n = 72$) %	p value
§ Abnormal feeling of fatigue (not caused by physical activity)	26.4	10.8	***	25.9	6.9	***
§ Balance disturbances or dizziness	13.6	3.9	***	11.2	5.6	*ns*
§ Concentration or memory difficulties	31.2	8.2	***	37.1	12.5	***
§ Problems sleeping all night	19.8	6.9	***	24.8	6.9	**
§ Repeated headaches	19.2	6.5	***	20.2	6.9	**
Awakening with a feeling of fatigue and exhaustion after a full night's sleep	25.2	11.3	***	28.7	8.3	***
Blurred vision not improved by the use of glasses	6.4	1.7	**	6.2	2.8	*ns*
Depression or sadness	22.6	10.4	***	23.1	16.7	*ns*
Disturbances of speech, trouble finding and pronouncing words correctly	12.7	3.9	***	15.4	9.7	*ns*
Feeling of nervousness, irritability or agitation	21.0	9.1	***	20.9	12.5	*ns*
Nightmares	8.6	3.5	**	5.6	5.5	*ns*
Numbness or tingling in hands or feet	14.1	7.8	**	16.1	4.1	**
Problems falling asleep	19.4	9.1	***	20.9	13.9	*ns*
Problems with fatigue lasting more than 24 hr after having made a physical effort	10.9	4.8	*	16.1	9.7	*
Suddenly diminished muscular power	2.5	0.4	*	3.5	0	—
Tingling or shivering of arms, legs or other parts of the body	9.0	3.0	**	11.9	2.8	*

Note. Shaded cells include results from larger Danish Study cohort (Table 3 in Ishoy et al., 1999). Columns 5–7 present the frequency of symptoms reported at the time of the larger study by the subset of Danish GW-deployed and non–GW-deployed troops that subsequently underwent neuropsychological testing.

§Identified relevant neuropsychological symptoms (Suadicani et al., 1999).

$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

Table V. Comparison of GW-Deployed and Non–GW-Deployed Troops on Neuropsychological Test Scores (Adjusted for Age)

Tests organized by functional domain	MANCOVA *p* value	Adj. *M* (*SE*) GW-deployed ($n = 143$)	Adj. *M* (*SE*) Non–GW-deployed ($n = 72$)	Univariate *p* value
Mood				
Profile of Mood States (POMS)	.009**			
Tension		7.5 (0.4)	6.2 (0.6)	.07
Depression		5.8 (0.5)	4.6 (0.8)	.21
Anger		6.6 (0.4)	5.7 (0.6)	.23
Fatigue		6.3 (0.4)	4.6 (0.5)	.005**
Confusion		5.9 (0.3)	4.1 (0.4)	.001**
Attention	.135			
CPT Overall, mean response latency		387.8 (3.4)	380.1 (4.8)	.20
Trail-making test, Part A, Response time		24.7 (0.6)	23.1 (0.9)	.14
Executive function	.066			
Trail-making test, Part B, Response time		63.6 (1.9)	56.6 (2.6)	.06
Wisconsin Card Sorting Test, # Correct		45.9 (0.7)	48.4 (1.0)	.05*
Wisconsin Card Sorting Test, # Categories		3.2 (0.1)	3.6 (0.2)	.02*
Motor skills	.940			
Purdue Pegboard, dominant hand		15.6 (0.1)	15.6 (0.2)	.93
Purdue Pegboard, nondominant hand		15.1 (0.1)	15.2 (0.2)	.67
Purdue Pegboard, both hands		12.9 (0.1)	12.9 (0.2)	.89
Visuospatial abilities				
WAIS-R Block Designs		39.1 (0.7)	40.6 (0.9)	.19
Verbal memory	.090			
CVLT Trial 1 Correct		6.2 (0.1)	6.7 (0.2)	.02*
CVLT Trial 5 Correct		12.0 (0.2)	12.7 (0.2)	.01**
CVLT List B Correct		5.6 (0.2)	6.1 (0.2)	.06
CVLT short delay, correct		10.7 (0.2)	11.3 (0.3)	.07
CVLT long delay, correct		11.1 (0.2)	11.6 (0.3)	.14
Visual memory	.313			
WMS, Visual Reproductions, Immediate recall		12.1 (0.2)	12.4 (0.2)	.37
WMS, Visual Reproductions, Delayed recall		11.5 (0.2)	11.9 (0.3)	.20

Note. WAIS-R= Wechsler Adult Intelligence Scale—Revised; CPT= Continuous Performance Test; CVLT= California Verbal Learning Test; POMS=Profile of Mood States; WMS= Wechsler Memory Scale.
*$p \leq .05$. **$p \leq .01$.

combat activities; bathing in or drinking contaminated water; depleted uranium, or contact with dead animals.

DISCUSSION

Findings from this study indicate that more mood complaints were observed among the Danish GW-deployed group than among the non–GW-deployed comparison group (specifically, higher levels of fatigue and confusion). However, significant differences for other specific neuropsychological domains were not seen. These results are similar to those observed by White et al. (2001) in a study of American GW veterans from the Devens Cohort Study, in which there was evidence of dysphoria but no widespread pattern of neuropsychological test differences in GW-deployed veterans compared to the non–GW-deployed group. Qualitative comparisons between the age-adjusted neuropsychological test scores of the Danish GW-deployed group and the American GW-deployed veterans (White et al., 2001) that can be compared directly (such as the time to complete Trail-making Test Part B, Purdue Pegboard, Wisconsin Card Sorting Test, WMS Visual Reproductions) indicate that the groups were generally similar, with the Danish GW-deployed group performing slightly better on some tasks. The Danish GW-deployed group demonstrated slightly higher mean *raw* scores on the WAIS-R Information subscale, but this may reflect different item content of the U.S. and Danish versions of the test.

It is possible that the significant differences in reporting of neuropsychological symptoms by the Danish GW-deployed group and the non–GW-deployed group had changed by the time of the objective neuropsychological testing, thus reducing the opportunity to observe significant differences in attention and memory function between

Table VI. Comparison of Non–GW-Deployed and GW-deployed Troops on Profile of Mood States (POMS) Fatigue and Confusion Subscale Scores (Adjusted for Age)

	Adj. *M* (*SE*)			
POMS subscale score	Non–GW-deployed ($n = 72$)	GW-deployed low + ($n = 74$)	GW-deployed medium ($n = 40$)	GW-deployed high ($n = 29$)
Fatigue	4.6 (0.5)	4.4 (0.5)	7.4 (0.6)[a]	9.2 (0.7)[a]
Confusion	4.1 (0.4)	4.2 (0.4)	6.8 (0.5)[a]	8.6 (0.6)[a]

Note. POMS = Profile of Mood States.
[a] $p \leq .01$, comparison between the adjusted means for the non–GW-deployed group and each of the respective GW-deployed groups.

the GW-deployed and non–GW-deployed groups. However, findings from other studies of GW-deployed veterans suggest that symptom reporting does not change dramatically over time. For example, no significant differences in the health symptom reporting by GW-deployed veterans over different 2–4-year time periods were observed within Devens Cohort Study members (Proctor et al., 1998; Wolfe, Proctor, Erickson, & Hu, 2002).

In this study of Danish veterans, neuropsychological deficits and self-reported symptoms of dysphoria were not tied to specific chemical exposures. Investigations of American veterans deployed to the GW, on the other hand, have shown associations between signs of CNS dysfunction and self-reported exposures to chemical warfare agents and to pesticides (White et al., 2001). Exposures to these agents were notably less frequent in the Danish GW-deployed group.

Comparisons between the frequencies of the 36 different GW service–related environmental exposures reported by the Danish study group and those reported by Devens Cohort Study members (Proctor et al., 1998) indicate that there are differences in the types of environmental exposures experienced by the two groups. This might be expected given the differences in deployment missions between the groups, because the Devens Cohort Study members were marshaled during the active combat period. For example, 67% of the Devens group of GW-deployed soldiers reported ingesting anti-nerve gas pills, while only 2% of the Danish GW-deployed indicated use of these pills. Also, 24% of the Devens group of GW-deployed soldiers reported exposure to chemical and/or biological warfare agents compared to only 0.7% of the Danish GW-deployed group.

In conclusion, results from this follow-up study of a subset of Danish GW-deployed veterans and non–GW-deployed military personnel suggest evidence of increased mood complaints related to GW service. However, no significant domain-specific evidence of CNS dysfunction was found. No associations between reported GW environmental exposures related to the Danish GW deployment mission and objective measures of cognitive functioning were observed.

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Neuropsychological Performance in Gulf War Era Veterans: Neuropsychological Symptom Reporting

Karen Lindem,[1,2,3] Susan P. Proctor,[1,3,6] Timothy Heeren,[1,4] Maxine Krengel,[1,2,3] Jennifer Vasterling,[8,9] Patricia B. Sutker,[9,11] Jessica Wolfe,[1,2,3,5,10] Terence M. Keane,[1,2,5,10] and Roberta F. White[1,2,3,5,6,7,12]

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Relationships between broad-based health symptoms and neuropsychological performance have been investigated previously in Gulf War (GW) veterans. However, very little has been done to assess relationships between severity of neuropsychological symptom complaints and performance on objective neuropsychological tests. In this study, relationships between level of self-reported neuropsychological symptom severity and objective neuropsychological performance measures were investigated. Participants included 240 veterans from three GW-era cohorts: GW-deployed veterans recruited from Ft. Devens, MA, ($n = 142$) and from New Orleans, LA ($n = 51$), and veterans deployed to Germany from a Maine National Guard unit ($n = 47$). Findings suggest that level of subjective neuropsychological complaints was associated primarily with mood symptoms in GW-era veterans. Among GW-deployed troops, high neuropsychological symptom reporters endorsed more tension, fatigue, and confusion and less vigor than those reporting fewer cognitive complaints. Current findings emphasize the importance of independent assessment of subjective symptoms and objective neuropsychological performance.

KEY WORDS: Gulf War syndrome; neuropsychological tests; health symptoms; cognitive symptoms.

Neuropsychological complaints of memory loss, diminished attention, and poor concentration are among the most commonly reported health complaints in Gulf War (GW) veterans (Proctor et al., 1998). Such cognitive complaints are also reported frequently in neurological, psychiatric, and general medical patients (Fox, Lees-Haley, Earnest, & Dolezal-Wood, 1995a, 1995b; Larrabee & Levin, 1986). Subjective cognitive complaints of poor concentration and memory may signify serious neurological impairment. However, subjective symptoms do not always correspond with objective measures of central nervous system (CNS) dysfunction. According to recent findings, patient populations have varying degrees of insight into cognitive functioning. Neuropsychological strengths and weaknesses may be underreported or overreported, depending on individual patient characteristics and level of neurological and neuropsychological dysfunction. Patients with Alzheimer's disease may have limited insight into their cognitive deficits (Seltzer, Vasterling, Hale, & Khurana, 1995), whereas patients with mild closed head injury often report more neuropsychological

[1]Boston Environmental Hazards Center, VA Boston Healthcare System, Boston, Massachusetts.
[2]VA Boston Healthcare System Medical Center, Psychology Department, Boston, Massachusetts.
[3]Department of Neurology, Boston University School of Medicine, Boston, Massachusetts.
[4]Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston, Massachusetts.
[5]Department of Psychology, Boston University, Boston, Massachusetts.
[6]Department of Environmental Health, Boston University School of Public Health, Boston, Massachusetts.
[7]University of Southern Denmark, Odense, Denmark.
[8]VA Medical Center, New Orleans, Louisiana.
[9]School of Medicine (Psychiatry and Neurology), Tulane University, New Orleans, Louisiana.
[10]Department of Psychiatry, Boston University School of Medicine, Boston, Massachusetts.
[11]Texas Tech University Health Sciences Center, Lubbock, Texas.
[12]To whom correspondence should be addressed at Boston Environmental Hazards Center, VA Boston Healthcare System Medical Center, 150 South Huntington Avenue (116B-4), Boston, Massachusetts 02130; e-mail: rwhite@bu.edu.

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complaints than are evident on testing (Binder & Willis, 1991).

The relationship between subjective cognitive complaints and objective test results in GW-deployed veterans remains unclear. Findings from early reports suggested that there was no evidence of neuropsychological dysfunction in GW-deployed veterans when controlling for "psychological factors" (Goldstein, Beers, Morrow, Shemansky, & Steinhauer, 1996; Sillanpaa et al., 1997). In contrast, other investigators concluded that there is evidence of generalized neuropsychological decline in GW-deployed veterans (Hom, Haley, & Kurt, 1997) or of specific types of deficits (Anger et al., 1999). Vasterling and colleagues (Vasterling, Brailey, Constans, Borges, & Sutker, 1997; Vasterling, Brailey, Constans, & Sutker, 1998) reported that neuropsychological deficits were evident in a sample of GW-deployed veterans who suffered from posttraumatic stress disorder (PTSD). In their sample, GW-deployed veterans diagnosed with PTSD differed from those without PTSD on several neuropsychological measures, including indices and subscales of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and tasks assessing sustained attention, mental manipulation, and initial acquisition of new information.

White et al. (2001), Proctor et al. (1998), Wolfe, Proctor, Davis, Borgos, and Friedman (1998), and Wolfe et al. (1999) have systematically investigated patterns of health symptom reporting, including neuropsychological symptoms, as well as objective performance on neuropsychological test measures in GW-era veterans. Findings from these studies confirm that GW-deployed veterans reported more subjective health symptoms than Germany-deployed GW-era veterans during the same time period (Proctor et al., 1998; Wolfe et al., 1998, 1999). In addition, health complaints were significantly associated with specific environmental exposures (Proctor et al., 1998). Self-reported exposures to environmental agents such as pesticides and chemical/biological warfare (CBW) agents were associated with frequency of neurological, neuropsychological, and psychological health symptom complaints, even when controlling for exposure to war-zone stressors and PTSD. Results from objective test measures suggest that self-reported exposure to pesticides was related to dysphoric symptomatology, whereas self-reported exposure to chemical warfare agents was associated with poorer performance on tests of attention and short-term memory. These studies suggest that environmental exposure and psychiatric status play significant roles in subjective health symptom reporting, as well as in performance on objective neuropsychological tests.

In addition to the investigations of White and colleagues, three reports from the Portland Environmental Hazards Center have investigated relationships between health symptom reporting, psychological distress, and neuropsychological performance in GW-deployed GW-era veterans (Anger et al., 1999; Binder et al., 1999, 2001). Anger et al. (1999) reported that GW-deployed veterans who reported elevated health complaints and more psychological distress performed more poorly and more slowly on a forced-choice recognition task than GW-deployed veterans with fewer health complaints and less psychological distress. A recent report by Binder et al. (2001) suggested that cognitive deficits were associated with chronic fatigue syndrome in a subsample of GW veterans. Both of these studies investigated associations between broad-spectrum symptom reporting involving a range of body systems (such as fatigue, muscle or joint pain, gastrointestinal symptoms, skin lesions, and psychological or cognitive complaints) and neuropsychological performance in GW-deployed veterans. Only one study to date has investigated the relationship between neuropsychological complaints, such as having difficulty concentrating or remembering, and objective test performance (Binder et al., 1999). Binder and colleagues reported that correlations between level of subjective cognitive complaints and performance on a computerized battery of cognitive tests were modest. In contrast, they reported that subjective cognitive complaints were more strongly associated with measures of affective distress, including both depression and anxiety.

The goal of this study was to investigate the relationship between level of neuropsychological symptom reporting and objective test performance in GW-era veterans using standardized neuropsychological performance measures across a full range of neuropsychological functions. To develop a more comprehensive understanding of neuropsychological health complaints in GW-era veterans, neuropsychological symptom severity was determined for three cohorts of GW-deployed and Germany-deployed GW-era veterans. Severity of neuropsychological symptoms was based on summary scores from five specific cognitive complaints taken from a 52-item health symptom questionnaire. The five neuropsychological symptoms, which were rated by participants on a likert scale, included difficulty concentrating, difficulty learning new material, forgetfulness, memory lapses, and confusion. It was predicted that participants who endorsed experiencing higher total levels of neuropsychological symptomatology would demonstrate poorer performance on neuropsychological tasks assessing attention (e.g., cognitive tracking, sustained attention, and cognitive flexibility) and memory functions (e.g., learning, spontaneous recall, and retrieval) relative to those with few or no cognitive complaints.

METHODS

A detailed description of the study protocol, participants, and measures has been outlined previously by Proctor et al. (1998), White et al. (2001), and Lindem et al. (2003). The current study was part of a larger center project investigating several outcome measures in GW veterans.

Participants

Participants in this study were 240 individuals from three cohorts of GW-era veterans. Veterans deployed to the Gulf were recruited from a group that returned from the Gulf to Ft. Devens, MA ($n = 142$) and to New Orleans, LA ($n = 51$). Veterans deployed to Germany were recruited from a Maine National Guard unit ($n = 47$).

Study Protocol and Measures

Participants completed and signed informed consent and were administered a battery of tests, including questionnaires, an environmental interview, a neuropsychological test battery, and two structured psychiatric interviews.

Demographics

Several demographic variables were collected, including age, highest educational level attained, race, gender, marital status, employment status, medication use, prior military service, and disability status.

Health Symptoms and Neuropsychological Complaints

Veterans completed the Expanded Health Symptom Checklist (HSC) as described by Proctor et al. (1998). A 20-item checklist of health symptoms (Bartone, Ursano, Wright, & Ingraham, 1989) was initially administered in the 1992/1993 survey. Subsequently, an expanded list of 52 items was developed to assess current health complaints and change in the original 20 items over time. Each of the 52 symptoms assessed was assigned to one of nine body systems (cardiac, pulmonary, dermatological, gastrointestinal, genitourinary, musculoskeletal, neurological, neuropsychological, and psychological) as described by Proctor et al. (1998). The HSC queried how often each of the 52 health symptoms was experienced over the 30 days prior to completion of the HSC. Responses were given on a 5-point scale (0 = *never*; 1 = *once or twice in all*; 2 = *about once/week*; 3 = *several times/week*; 4 = *almost every day*).

Neuropsychological Symptom Severity

Severity of neuropsychological symptoms was determined from a subset of five items from the 52-item HSC. The five health symptoms from the HSC classified as neuropsychological symptom complaints included difficulty concentrating, difficulty learning new material, forgetting, memory lapses, and confusion. Participants were queried about how often each of the five symptoms was experienced over the 30 days prior to completion of the HSC. Responses were given on a 5-point scale (0 = *never*; 1 = *once or twice in all*; 2 = *about once/week*; 3 = *several times/week*; 4 = *almost every day*). The frequency scores for each of the five neuropsychological symptoms were summed to determine an overall score assessing severity of total neuropsychological complaints, with a range of possible scores from 0 to 20.

Neuropsychological Test Battery

The neuropsychological test battery assessed abilities in the functional domains of general intelligence, attention/executive function, motor ability, visuospatial processing, verbal and visual memory, mood, and motivation. The battery required approximately 2 hr to complete, and the order of task presentation was the same for all veterans. To assess general intellectual ability, the Information subscale (age-scaled score) of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) was administered. Attention and executive functions were assessed using WAIS-R; Digit Span (total raw score, forward digit span, backward digit span; Wechsler, 1981); Wechsler Memory Scale-Revised Digit Span (forward raw score, forward digit span, backward raw score, backward digit span; WMS-R; Wechsler, 1987); the Neurobehavioral Evaluation System Continuous Performance Task (total scores mean reaction time, median reaction time, standard deviation, false positives, nonresponses; CPT; Letz, 1991); Trail-making Test A and B (Trails A time in seconds, Trails B time in seconds, errors A, errors B, total errors; Halstead, 1947); Wisconsin Card Sorting Test (number of successful sorts, number of errors; WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993); Paced Auditory Serial Addition Test (number correct on trial 1, trial 2, trial 3, and trial 4; PASAT; Gronwall, 1977).

To assess motor and psychomotor performance the Finger Tapping Test (dominant hand 5 trial mean, nondominant hand 5 trial mean; Halstead, 1947) and the Purdue Pegboard (dominant hand number correct, nondominant hand number correct, extra trials; Purdue Research Foundation, 1948) were administered. Visuospatial

constructional abilities were assessed with the WAIS-R Block Design (age-scaled score). Verbal memory abilities were assessed with the WMS-R Verbal Paired Associate Learning (easy items immediate recall, easy items delayed recall, difficult items immediate recall, difficult items delayed recall, total immediate recall, total delayed recall; Wechsler, 1987) and the California Verbal Learning Test (trials 1–5: total number correct, clusters, perseveration, intrusions; Tuesday list number correct, clusters, perseveration, intrusions; short delay recall number correct, clusters, perseveration, intrusions; short delay cued recall number correct, clusters, perseveration, intrusions; long delay recall number correct, clusters, perseveration, intrusions; long delay cued recall number correct, clusters, perseveration, intrusions; number correct on recognition; CVLT; Delis, Kramer, Kaplan, & Ober, 1987). Memory for visuospatial material was assessed with Wechsler Memory Scale Visual Reproduction subtest (immediate recall, delayed recall, recognition, copy; WMS; Wechsler, 1945). Mood and motivation were assessed with the Profile of Mood States (*t* scores for Tension, Depression, Anger, Fatigue, Confusion, Vigor; POMS; McNair, Lorr, & Droppleman, 1971) and the Test of Memory Malingering (trial 1 number correct; TOMM; Tombaugh, 1996).

Psychiatric Status

Psychiatric status was established for each veteran based on four measures: the Structured Clinical Interview for DSM-III-R (SCID; Spitzer, Williams, Gibbon, & First, 1990), the Clinician Administered PTSD Scale (CAPS; Blake et al., 1990), the Mississippi Scale for Desert Storm War Zone Personnel (Keane, Caddel, & Taylor 1988), and the Brief Symptom Inventory (Derogatis, 1993). The SCID and CAPS were used as covariates in the current study.

Data Analyses

Neuropsychological symptom severity was determined, as described above, from a subset of five neuropsychological symptoms from the HSC. The sum across the five symptoms was used to determine symptom severity and categorize participants into one of three symptom levels: those with no cognitive complaints and a score of 0 (35.6% of sample), those with a moderate level of complaints (score of 1–4, 31.2% of sample), and those with a high level of complaints (score of 5–20, 33.2% of sample). The majority (66.8%) of the sample reported fewer than five cognitive symptoms (<5 symptoms), while 33.2% of the sample scored five or more symptoms (≥5 symptoms).

To explore the relationship between level of neuropsychological symptom reporting and objective neuropsychological performance, between group comparisons between participants with no, moderate, and high levels of cognitive symptoms were conducted for all neuropsychological performance variables. Data were analyzed in two steps. First, to control for multiple comparisons, neuropsychological test variables were grouped by test and domain, and MANCOVAs were performed to test for overall effects. Second, for all MANCOVAs that were found to be significant ($p < .05$), univariate linear regression analyses were performed to compare neuropsychological performance in GW-deployed and Germany-deployed veterans who reported a high level of cognitive complaints versus those who reported few or no cognitive complaints on the HSC. Univariate regression analyses and MANCOVAs were carried out controlling for the potential contributions of age, education, WAIS-R Information Age-Scaled score, deployment status (GW or Germany), medical conditions (history closed head injury, alcohol problems, diabetes, seizure disorder, and cancer), PTSD severity based on the CAPS, and depression at the time of assessment based on the SCID.

To control for the large number of analyses performed, data were screened for significance at three levels. Results for each neuropsychological outcome variable were included in tables only if the overall MANCOVA was significant ($p \leq .05$), the overall univariate model was significant ($p \leq .05$), and the independent grouping variable within the univariate analysis was significant ($p \leq .05$).

RESULTS

Results from the MANCOVA and univariate analyses investigating the relationship between level of neuropsychological complaints and neuropsychological performance are presented in Tables I and II. Table I presents results for GW-deployed and Germany-deployed groups combined, controlling for age, education, WAIS-R Information age-scaled score, medical conditions (closed head injury, history of alcohol problems, diabetes, seizure disorder, and cancer), PTSD severity, and depression. Univariate analyses demonstrated a significant relationship between level of neuropsychological symptom reporting and neuropsychological performance on a self-report measure of mood. A significant relationship between level of neuropsychological symptom reporting and neuropsychological performance was evident on all subscores of the POMS except Depression (Tension, Anger, Fatigue, Confusion, and Vigor).

Results for individual comparisons between the three groups—those with no cognitive complaints

Table I. Relationship Between Low, Moderate, and High Neuropsychological Symptom Complaints and Performance on Neuropsychological Test Measures in GW-Deployed and Germany-Deployed Veterans[a]

Tests organized by functional domain	*n*	MANCOVA[c] *p* value	Neuropsychological symptom groups[b] [Adjusted mean (*SE*)] Low (*n* = 66)	Moderate (*n* = 59)	High (*n* = 65)	Univariate *F* (2, 176)	*p* value	Low vs. Mod	Low vs. High	Mod vs. High
Mood										
Profile of mood states	190	.000**								
Tension, *t* score			35.94 (0.77)	37.36 (0.79)	40.49 (0.79)	7.9	.001**	0.203	0.000**	0.006**
Anger, *t* score			42.49 (0.86)	43.22 (0.87)	46.23 (0.88)	4.7	.010*	0.556	0.004**	0.018*
Fatigue, *t* score			43.46 (0.91)	45.27 (0.93)	50.25 (0.93)	13.0	.000**	0.169	0.000**	0.000**
Confusion, *t* score			37.12 (0.66)	39.86 (0.67)	44.38 (0.68)	26.9	.000**	0.004**	0.000**	0.000**
Vigor, *t* score			59.74 (1.16)	57.59 (1.18)	55.09 (1.18)	8.5	.031*	0.197	0.008**	0.145

Note. GW = Gulf War. PTSD = posttraumatic stress disorder. WAIS-R = Wechsler Adult Intelligence Scale—Revised. CAPS = Clinician Administered PTSD Scale. WMS-R = Wechsler Memory Scale-Revised.

[a]all comparisons controlled for age, education, deployment status, WAIS-R Information age-scaled score, depression, PTSD, and history of closed head injury, alcohol abuse, diabetes, seizure disorder, and cancer.

[b]low = 0 symptoms, moderate = 1–4 symptoms, high = 5 or more symptoms.

[c]Scales administered and not found to differ by symptom level were, WAIS-R Digit Span (total raw score, forward span, backward span); WMS-R Digit Span (forward raw score, forward span, backward raw score, backward span); Continuous Performance Test (total scores: mean, median, standard deviation, false positives, nonresponses); Paced Auditory Serial Addition Test (number correct trials 1–4); Wisconsin Card Sorting Test (correct sorts, errors); California Verbal Learning Test (all variables); WMS-R Verbal Paired Associate Learning (all variables), WMS-R Visual Reproduction (all variables).

*$p < .05$. **$p < .01$.

(0 symptoms), those with few complaints (score of 1–4), and those with many complaints (score of ≥5)—are also presented in Table I. Between group comparisons between participants with no cognitive complaints (score of 0) and those with many complaints (≥5 score) demonstrated significant between group differences on all subscales of the POMS except Depression. Participants with no symptom complaints reported less Tension, Anger, and Fatigue but more Vigor on the POMS, relative to veterans with high scores. Between group comparisons of participants

Table II. Relationship Between Low, Moderate, and High Neuropsychological Symptom Complaints and Performance on Neuropsychological Test Measures in GW-Deployed Veterans[a]

Tests organized by functional domain	*n*	MANCOVA[c] *p* value	Neuropsychological symptom groups[b] [Adjusted mean (*SE*)] Low (*n* = 39)	Moderate (*n* = 49)	High (*n* = 61)	Univariate *F* (2, 137)	*p* value	Low vs. Mod	Low vs. High	Mod vs. High
Mood										
Profile of mood states	149	.000*								
Tension, *t* score			35.98 (1.01)	37.52 (0.89)	41.06 (0.83)	7.8	.001**	0.251	0.000**	0.005**
Fatigue, *t* score			44.17 (1.25)	45.67 (1.10)	50.75 (1.02)	8.9	.000**	0.364	0.000**	0.001**
Confusion, *t* score			37.51 (0.90)	40.11 (0.79)	44.93 (0.73)	20.3	.000**	0.030*	0.000**	0.000**
Vigor, *t* score			58.99 (1.53)	56.93 (1.35)	53.73 (1.25)	3.4	.035*	0.309	0.011*	0.093

Note. GW = Gulf War. PTSD = posttraumatic stress disorder. WAIS-R = Wechsler Adult Intelligence Scale—Revised. CAPS = Clinician Administered PTSD Scale. WMS = Wechsler Memory Scale.

[a]all comparisons controlled for age, education, WAIS-R Information age-scaled score, depression, PTSD severity, and history of closed head injury, alcohol abuse, diabetes, seizure disorder, and cancer.

[b]low = 0 symptoms, moderate = 1–4 symptoms, high = 5 or more symptoms.

[c]Scales administered and not found to differ by symptom level were, WAIS-R Digit Span (total raw score, forward span, backward span); WMS-R Digit Span (forward raw score, forward span, backward raw score, backward span); Continuous Performance Test (total scores: mean, median, standard deviation, false positives, nonresponses); Paced Auditory Serial Addition Test (number correct trials 1–4); Wisconsin Card Sorting Test (correct sorts, errors); California Verbal Learning Test (all variables); WMS-R Verbal Paired Associate Learning (all variables), WMS-R Visual Reproduction (all variables).

*$p < .05$. **$p < .01$.

with few cognitive complaints (score of 1–4) and those with many complaints (≥5) were similar. Individual comparisons demonstrated significant between group differences on all subscales of the POMS except Depression and Vigor. Participants with many cognitive complaints reported more Tension, Anger, and Fatigue on the POMS relative to those with fewer symptoms. No other significant between group differences were evident.

Comparisons between GW-deployed and Germany-deployed veterans revealed that the severity of neuropsychological symptoms endorsed by GW-deployed veterans was significantly greater than for Germany-deployed veterans (GW-deployed mean symptom score = 4.3, $SD = 4.9$; Germany-deployed mean symptom score = 1.3, $SD = 2.4$; $t = -5.9$, $p = .000$). When MANCOVA and univariate analyses were performed on GW-deployed veterans alone, a significant relationship was evident between level of symptom reporting and mood complaints (see Table II). GW-deployed veterans with no cognitive complaints endorsed significantly less confusion on mood testing relative to veterans reporting medium- and high-levels of neuropsychological symptoms. Veterans with high levels of symptoms endorsed more tension, fatigue, confusion and less vigor than those with lower levels of symptoms or no cognitive complaints.

Analyses of neuropsychological symptom reporting in Germany-deployed ($n = 49$) veterans demonstrated no significant results. Few participants scored ≥5 out of 20. Twenty-seven participants reported no symptoms, 10 participants received scores of 0–4, and 4 participants received scores of ≥5. Because of these small numbers, particularly in the high symptom group, none of the MANCOVA analyses resulted in significant findings.

DISCUSSION

The Persian Gulf Veterans Coordinating Board (1995) reported that of the 17, 248 ill or concerned Gulf-deployed veterans enrolled in the VA Persian Gulf War Registry at that time, 10.5% reported neuropsychological complaints, including difficulty concentrating, forgetfulness, irritability, and depression. On the basis of clinical examination, Bourdette et al. (2001) found that 87% (212 out of 244) of symptomatic veterans endorsed experiencing cognitive and psychological symptoms, with 73% (152 out of 209) reporting memory or concentration difficulties. Neuropsychological symptom reporting was addressed in the current study to develop a better understanding of the relationship between cognitive complaints and objective neuropsychological performance in GW veterans.

The findings of this study suggested that level of subjective cognitive complaints was not associated consistently with objective performance deficits in the predicted domains of attention or memory. Rather, level of subjective cognitive complaints in GW-deployed and Germany-deployed veterans was associated primarily with mood complaints. These findings are consistent with those reported by Binder et al. (1999), who showed that subjective cognitive complaints among GW veterans were more strongly associated with affective distress than with objective performance deficits on computer-assisted tests in a smaller sample of GW veterans.

Findings reported by Gass and Apple (1997) and others (Binder et al., 1999; Williams, Little, Scates, & Blockman, 1987) suggest that some patient populations fail to differentiate between mood and cognitive complaints. Depressed patients tend to report more cognitive complaints, including increased frequency and severity of memory complaints, than nondepressed control participants (Williams et al., 1987). However, poor performance on objective tests of attention and concentration is often observed in patients with depression (Lezak, 1995). The attention problems, concentration difficulties, and distractibility seen in some patient populations, such as those with mild head injury and depression, are frequently interpreted as "memory" problems. Although attentional problems involving poor tracking and distractibility may be identified during testing, significant memory deficits involving loss of learned material over delays (forgetting) are typically not evident on formal testing.

In this study, the finding that a high level of subjective cognitive complaints was significantly associated with mood complaints rather than poorer performance on objective neuropsychological tests of cognition suggests that participants did not differentiate between mood and cognitive symptoms. Results then are consistent with the conclusion that attention and memory complaints can be seen in association with affective distress, which in turn may negatively impact cognitive test performance (Gass, 1996).

The current findings underline the necessity of obtaining independent assessment of cognitive function through the use of objective neuropsychological test methods in persons complaining of cognitive problems. Results suggest that level of cognitive complaints may not correspond to observable deficits in cognitive function. At the same time, results obtained in the current work do not suggest that deficits are absent in this population. There is considerable evidence to suggest that lower scores on neuropsychological tests in GW-deployed veterans can be observed and are associated with factors such as PTSD and environmental exposure to hazardous agents (Lindem et al., 2003; White et al., 2001). Therefore, appropriate assessment of *both* mood and neuropsychological

factors is necessary among veterans reporting cognitive complaints. The current findings emphasize the necessity of utilizing objective neuropsychological assessment methods when making diagnostic decisions about veteran and other patient populations and planning appropriate treatment interventions.

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Neuropsychological Performance in Gulf War Era Veterans: Motivational Factors and Effort

Karen Lindem,[1,2,3] Roberta F. White,[1,2,3,5,6,7,12] Timothy Heeren,[1,4] Susan P. Proctor,[1,3,6] Maxine Krengel,[1,2,3] Jennifer Vasterling,[8,9] Jessica Wolfe,[1,2,3,5,10] Patricia B. Sutker,[9,11] Shalene Kirkley,[1] and Terence M. Keane[1,2,5,10]

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Assuming that the underlying etiology of unexplained health-related symptoms in returning Gulf War (GW) veterans is multifactorial, the possible role of feigning or exaggeration of symptoms is worth consideration as a contributing factor. The present study assessed the relationship between motivation to perform well during neuropsychological assessment and objective neuropsychological test performance. Motivation was measured as the score on a visual memory task (Test of Memory Malingering, TOMM) of low difficulty. Participants included 77 veterans from the cohorts of GW- ($n = 58$) and Germany-deployed ($n = 19$) GW-era veterans described in two other papers in this issue who were administered the TOMM. Most veterans earned perfect or near-perfect scores on the TOMM (48–50/50). Scores ≤ 47 were associated with lower scores on neuropsychological tasks assessing attention, executive functions, and memory. Variability in test performance within and between tasks measuring similar functions was also found in participants with lower TOMM scores.

KEY WORDS: Gulf War syndrome; neuropsychological tests; motivation; malingering.

Fabrication, exaggeration, or misattribution of health-related symptoms are defining features of conditions which have been viewed as strongly influenced by motivational factors. The intentional production or exaggeration of health symptoms linked to external incentives, such as obtaining financial compensation, has been described in the *DSM-IV* as a condition which may be the focus of clinical attention, such as malingering (Diagnostic and statistical manual of mental disorders, fourth edition, *DSM-IV*, V65.2, 1994). Nonexistent symptoms may be fabricated completely in some cases. However, presentation of fabrication or exaggeration is difficult to discriminate, particularly when health-related symptoms are exaggerated subtly to varying degrees or attributed to unrelated causes (Rogers, 1990). Thus, presentation of motivationally related health problems and behaviors is a complex phenomenon, difficult to detect and to characterize.

Identification of motivational conditions is complicated by the severity and type of the health-related symptom that is under consideration. For this study, motivation is discussed as related to a specific health outcome in the veteran population that served during the Gulf War (GW) era, namely the relationship between motivation to perform well during neuropsychological assessment and scores on objective tests. As with all clinical issues,

[1]Boston Environmental Hazards Center, VA Boston Healthcare System, Boston, Massachusetts.
[2]Psychology Department, VA Boston Healthcare System Medical Center, Boston, Massachusetts.
[3]Department of Neurology, Boston University School of Medicine, Boston, Massachusetts.
[4]Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston, Massachusetts.
[5]Department of Psychology, Boston University, Boston, Massachusetts.
[6]Department of Environmental Health, Boston University School of Public Health, Boston, Massachusetts.
[7]University of Southern Denmark, Odense, Denmark.
[8]VA Medical Center, New Orleans, Louisiana.
[9]School of Medicine (Psychiatry and Neurology), Tulane University, New Orleans, Louisiana.
[10]Department of Psychiatry, Boston University School of Medicine, Boston, Massachusetts.
[11]Texas Tech University Health Sciences Center, Lubbock, Texas.
[12]To whom correspondence should be addressed at Boston Environmental Hazards Center, VA Boston Healthcare System Medical Center, 150 South Huntington Avenue (116B-4), Boston, Massachusetts 02130; e-mail: rwhite@bu.edu.

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motivational variables must be addressed cautiously and with significant respect for patient concerns and multiple factors, many of which continue to remain unknown, that have contributed to illness presentation in this population. To date, no single factor, or interaction of variables, has fully and clearly explained the extent or range of health-related symptoms endorsed by veterans who saw duty in the GW zone. Since the underlying etiology is likely to be multifactorial, an in-depth understanding of how motivational issues contribute to illness presentation in the GW-era veteran population is an important diagnostic step.

Assessment of neuropsychological function is used often to identify the functional status of the central nervous system (CNS) associated with normal aging and with neurological, general medical, and psychiatric disorders (Lezak, 1995). Patterns of neuropsychological performance have been studied extensively to map brain-behavior relationships associated with known illnesses and disorders. Neuropsychological assessment, as a sensitive indicator of the integrity of the CNS, is therefore well-suited to identify the test variability and inconsistent performances that are hallmarks of motivationally related health behaviors (Binder, 1993; Iverson & Binder, 2000; Reitan & Wolfson, 1997; Tombaugh, 1996). A number of factors, including psychiatric status, or the desire to obtain treatment, avoid stressors, or obtain financial compensation, may contribute to inconsistent performance and variable effort on neuropsychological testing in specific patient populations (Binder, 1997; Binder & Willis, 1991; Green, Rohling, Lees-Haley, & Allen, 2001; Tombaugh, 1996).

External factors are known to affect health behaviors in many patient populations, and external incentives have long been considered relevant among war veterans (Nies & Sweet, 1994). Despite the relevance of this clinical issue, motivational concerns in GW veterans have not been addressed extensively in the literature. Four studies have included measures of motivation in investigations of GW-related illnesses (Anger et al., 1999; Binder et al., 2001; Hom, Haley, & Kurt, 1997; White et al., 2001). Hom et al. (1997) reported no significant difference between GW-deployed veterans and controls on a measure of motivation from a self-report personality assessment (Personality Assessment Inventory). In contrast, Anger et al. (1999) reported that GW-deployed veterans with self-reported GW-related health symptoms performed more poorly than GW-deployed veterans without health complaints on a computer-assisted, forced-choice test of motivation, attention, and memory (Oregon Dual Task Procedure, ODTP; Anger et al., 1996). Although all veterans correctly identified more than 80% of items on the ODTP, GW-deployed veterans with health complaints identified significantly fewer correct responses than those without health complaints. In addition, a subset of participants was identified that exhibited specific neurobehavioral deficits, such as response slowing, which were not evident in other veterans.

Similar findings were reported recently by Binder et al. (2001), who identified a subgroup of veterans with chronic fatigue syndrome (CFS). GW-deployed veterans with CFS made more errors on the ODTP forced-choice task and demonstrated slower reaction times and response latencies relative to control participants. In a separate study, White et al. (2001) reported that GW-deployed veterans who reported exposure to chemical warfare agents scored lower than GW-deployed veterans with no self-reported chemical warfare agent exposure on a test of motivation (Test of Memory Malingering, TOMM). However, controlling for TOMM scores in the data analyses did not change the significant exposure–function relationships identified among GW-deployed veterans. Overall, results published by Anger et al. (1999), Binder et al. (2001), and White et al. (2001) suggest that variable motivation or effort is not the primary contributing factor to neuropsychological performance deficits observed in GW-deployed veterans with health complaints of undetermined etiology. However, findings do suggest that motivation to perform well may contribute to neuropsychological performance patterns observed in a subgroup of the samples studied.

Qualitative and quantitative strategies for assessing motivational deficits in neuropsychological assessment have been outlined by White, Feldman, and Proctor (1992) and by Tombaugh (1996). Performance on tasks measuring specific cognitive domains can be assessed for relative performance differences between and within tasks to provide evidence of inconsistent performance, variable effort, and noncompliance during assessment. Noncompliance or variable effort may be suggested when performance is better on a difficult task relative to an easier task or trial, when performance differs on the same test given more than once, or when performance is impaired on "hold tests" that is, tasks which assess overlearned knowledge and therefore are the most resistant to neurological dysfunction. In addition, errors made during neuropsychological assessment, such as false positive responses, approximate answers, and nonresponding, may also suggest variable effort.

In the current study, motivation to perform well on neuropsychological testing was assessed in veterans who served in the GW-era using the TOMM, an instrument which has been found to be effective in identifying malingering in research and clinical populations (Rees, Tombaugh, Gansler, & Moczynski, 1998; Tombaugh, 1996). In addition, measures of inconsistent performance were applied to a broad neuropsychological evaluation

based on the strategies suggested by Liebsen, White, and Albert (1996), White et al. (1992), White and Rose (1996), and Tombaugh (1996).

High rates of motivational disorders were not expected. However, it was hypothesized that scores on the TOMM would contribute to scores on cognitive tests (i.e., to lower test scores). Specifically, significant differences between highly motivated and poorly motivated veterans were expected across tasks assessing all neuropsychological domains. Since the TOMM has been shown to be particularly effective in assessing memory malingering, significant performance differences were hypothesized to be most evident on standard outcome measures that assessed memory (e.g., WMS-R Verbal Paired Associate Learning, California Verbal Learning Test, WMS Visual Reproduction) and tasks characterized by face validity as tests of memory, (e.g., WAIS-R Information and Digit Span; Tombaugh, 1996).

METHODS

The current study was part of a larger center project investigating several outcome measures in GW-era veterans. Participants completed and signed informed consent and were administered a battery of tests including questionnaires, an environmental interview, a neuropsychological test battery, and two structured psychiatric interviews. A detailed description of the study protocol, participants and measures has been outlined previously by Proctor et al. (1998) and by Lindem et al. (2003).

Participants and Recruitment

To investigate the relationship between motivation to perform well on testing and measured neuropsychological performance, the TOMM was added to a comprehensive battery of neuropsychological tests that was being administered to cohorts of GW-era veterans who served in the Gulf and elsewhere. Because this test was added after the investigation was underway, only subsets of the GW-era veteran samples who were tested at the later time point completed the instrument.

Participants included 77 veterans drawn from two groups of GW-era troops who completed the TOMM as part of a comprehensive behavioral assessment. These included veterans deployed to the GW who returned to Ft. Devens, MA ($n = 58$) and veterans from a Maine National Guard unit who were deployed to Germany during the war ($n = 19$). To evaluate relationships between TOMM performance and neuropsychological test scores, GW-deployed veterans who scored high on the TOMM (48–50/50) were compared to those who scored lower on the TOMM ($\leq$47). Data from the GW-deployed cohort and the Germany-deployed cohort were then combined and analyzed in order to maximize capacity to evaluate relationships between TOMM scores and neuropsychological test measures as clearly as possible.

Study Protocol and Measures

Demographics

Data on several demographic variables were collected, including age, highest educational level attained, race, gender, marital status, employment status, medication use, prior military service, and disability status.

Neuropsychological Test Battery

The neuropsychological test battery assessed abilities in the functional domains of general intelligence, attention/executive function, motor ability, visuospatial processing, verbal and visual memory, mood and motivation. The battery required approximately 2 hr to complete, and the order of presentation of tasks was fixed for all participants. To assess general intellectual ability, the Information subscale (age-scaled score) of the Wechsler Adult Intelligence Scale – Revised (Wechsler, 1981) was administered. Attention and executive functions were assessed using WAIS-R Digit Span (total raw score, forward digit span, backward digit span; Wechsler, 1981); Wechsler Memory Scale – Revised Digit Span (forward raw score, forward digit span, backward raw score, backward digit span; WMS-R; Wechsler, 1987); the Neurobehavioral Evaluation System Continuous Performance Task (total scores mean reaction time, median reaction time, standard deviation, false positives, nonresponses; CPT; Letz, 1991); Trail-making Tests A and B (Trails A time in seconds, Trails B time in seconds, Errors A, Errors B, total errors; Halstead, 1947); Wisconsin Card Sorting Test (number of successful sorts, number of errors; WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993); Paced Auditory Serial Addition Test (number correct on Trial 1, Trial 2, Trial 3, and Trial 4; PASAT; Gronwall, 1977). To assess motor and psychomotor performance, the Finger Tapping Test (dominant hand 5 trial mean, nondominant hand 5 trial mean; Halstead, 1947) and the Purdue Pegboard (dominant hand number correct, nondominant hand number correct, extra trials; Purdue Research Foundation, 1948) were administered. Visuospatial constructional abilities were assessed with the WAIS-R Block Design (age-scaled score).

Verbal memory abilities were tested with the WMS-R Verbal Paired Associate Learning (easy items immediate

recall, easy items delayed recall, difficult items immediate recall, difficult items delayed recall, total immediate recall, total delayed recall; Wechsler, 1987) and the California Verbal Learning Test (Trials 1–5: total number correct, clusters, perseveration, intrusions; Tuesday list number correct, clusters, perseveration, intrusions; short delay recall number correct, clusters, perseveration, intrusions; short delay cued recall number correct, clusters, perseveration, intrusions; long delay recall number correct, clusters, perseveration, intrusions; long delay cued recall number correct, clusters, perseveration, intrusions; number correct on recognition; CVLT; Delis, Kramer, Kaplan, & Ober, 1987). Memory for visuospatial material was assessed with Wechsler Memory Scale Visual Reproduction (immediate recall, delayed recall, recognition, copy; WMS; Wechsler, 1945). Mood was assessed with the Profile of Mood States (T-scores for Tension, Depression, Anger, Fatigue, Confusion, Vigor; POMS; McNair, Lorr, & Droppleman, 1971).

Motivation and Effort

Outcome measures established for the current study were based on standard administration of all test instruments. Additional scoring techniques and strategies were included to assess inconsistent performance and variable effort during testing. Measures of inconsistent performance included relative performance differences (e.g., difference scores between easy and difficult tasks), several measures of error types (e.g., frequency scores for approximate answers and nonresponses), comparison of performance on hold tests (e.g., WAIS-R Information) and comparison of performance on tests least expected to be affected by CNS injury (e.g., Digit Span Forward).

The Test of Memory Malingering (TOMM; Tombaugh, 1996) was administered as an objective measure of effort to perform well on cognitive tasks. In the standard administration of the test, three trials are administered (two immediate recall recognition trials and a retention trial), with the clinical cut-off score for diagnosis of possible motivational disorder being 45 on Trial 2. For this study, only Trial 1 was administered. In part, administration was changed to save time, but the decision was also based on clinical experience indicating that performance on Trial 1 is better related to other signs of inconsistent performance or unwillingness to perform optimally across all tasks in a neuropsychological battery than that on Trials 2 or 3 (R. F. White, personal communication, January 2000). Participants were categorized as high (48–50) or low ($\leq$47) scorers based on total number correct on Trial 1. The decision to use 47 as the dividing line between high and low scorers on the TOMM was based also on this experience, which suggests that the criterion of 45 is a very conservative cut-off (i.e., it results in false negatives for poor motivation) and on the desire to compare *suboptimal* effort to *optimal* effort when examining the relationships between TOMM-measured motivation to perform well and neuropsychological test scores.

Psychiatric Status

Psychiatric status was established for each veteran using two measures: the Structured Clinical Interview for *DSM-III-R* (SCID; Spitzer, Williams, Gibbon, & First, 1990) and the Clinician Administered PTSD Scale (CAPS; Blake et al., 1990). These instruments yielded a range of Axis I disorder diagnoses. Current and lifetime diagnoses of PTSD and depression were considered pertinent to this study.

Health Symptoms

Veterans completed the Expanded Health Symptom Checklist (HSC) described by Proctor et al. (1998), a 52-item expanded version of the original 20-item checklist of health symptoms (Bartone, Ursano, Wright, & Ingraham, 1989) used in the 1992/1993 survey. The HSC determined how often 52 health symptoms were experienced over the 30 days prior to response to the HSC. Symptoms from 9 body systems were assessed (cardiac, pulmonary, dermatological, gastrointestinal, genitourinary, musculoskeletal, neurological, neuropsychological, and psychological). Responses were given on a 5-point scale (0 = *never*; 1 = *once or twice in all*; 2 = *about once/week*; 3 = *several times/week*, 4 = *almost every day*).

Data Analysis

Performance on the TOMM (Tombaugh, 1996) was used to categorize veterans into two groups based on a maximum score of 50 points. The high-scoring group of GW-deployed veterans ($n = 40$) consisted of participants whose performance was considered to be optimal or near-perfect (48–50 points). The low-scoring GW-deployed group ($n = 18$) included veterans whose performance was less than optimal ($\leq$47 points). Between group comparisons of demographic variables and veteran characteristics for the high- and low-scoring groups were completed. Student's t test was used for comparisons of differences in mean scores for continuous variables, and the χ^2 statistic was used for comparisons of differences in proportions for categorical variables.

Individual univariate regression analyses were performed to compare neuropsychological test performance

in GW-deployed veterans who scored ≤47 on the TOMM versus those who performed better. To control for multiple comparisons, neuropsychological variables were grouped by test and domain and MANCOVAs were performed on grouped variables to test for overall effects. For all of those found to be significant ($p < .05$), individual univariate regression analyses were performed to compare neuropsychological test performance in the high- versus low-scoring groups. Adjusted mean scores on neuropsychological test variables were compared for veterans who scored 47 points or less to those who performed well, or earned 48–50 points. Covariates included age and education.

Between group comparisons were made between the GW-deployed cohort and the Germany-deployed GW-era veterans. The two cohorts were compared on the mean score on the TOMM and the number of participants who scored suboptimally. The sample was then combined as a GW-era sample (i.e., GW-deployed and Germany-deployed veterans). Performance on the TOMM was again used to categorize all participants into two groups (high scoring and low scoring). Individual univariate regression analyses were then performed to compare neuropsychological test performance in the combined sample of high (48–50) and low (≤47) scorers. To control for multiple comparisons, neuropsychological variables were grouped by test and domain, and MANCOVAs were performed on grouped variables to test for overall effects. For all of MANCOVA results found to be significant ($p < .05$), individual univariate regression analyses were performed to compare neuropsychological test performance in the high- versus low-scoring groups. Adjusted mean scores on neuropsychological test variables were compared for the high and low scoring groups. Covariates used in these analyses with the larger combined sample included age, education, WAIS-R Information Age-Scaled score, deployment status (Gulf or Germany), and PTSD symptomatology (CAPS severity score).

RESULTS

Comparisons of demographic variables and participant characteristics between GW-deployed veterans who scored ≤47 versus those who scored ≥48 are presented in Table I. No statistically significant differences in age, education, or general intellectual ability as measured by the WAIS-R Information subtest, were evident between those who scored low and those who scored high on the TOMM. No between group differences were evident for current or lifetime diagnoses of depression as assessed using the SCID. They did not differ on current or lifetime PTSD diagnoses or with regard to most self-reported health-related symptoms. However, those who scored lower on the TOMM endorsed a greater number of cardiac symptoms.

Results from the MANCOVA and univariate analyses investigating the relationship between level of performance on the TOMM and neuropsychological performance in GW-deployed veterans are presented in Table II. To control for the large number of analyses performed, data were screened for significance at three levels. Results for each neuropsychological outcome variable were included in tables only if the overall MANCOVA was significant ($p < .05$), the overall univariate model was significant ($p < .05$), and the independent grouping variable within the univariate analysis was significant ($p < .05$).

Univariate regression analyses controlling for age and education showed a significant relationship between performance on the TOMM and neuropsychological test scores on tasks assessing attention/executive system functions and memory. Age and education are considered to account for a portion of variance associated with premorbid intellectual function, which contributes to performance on many neuropsychological tests. Therefore, age and education were included as covariates despite no significant between group differences. Results revealed that GW-deployed veterans who obtained lower scores on the TOMM scored significantly lower scores on certain performance measures from the WCST (number of correct sorts), WMS-R Verbal Paired Associate Learning (total immediate recall), and CVLT (cued long delay recall).

Table III provides a comparison of TOMM scores between the GW-deployed cohort and the Germany-deployed GW-era cohort. There was no significant difference in mean TOMM scores between the two cohorts. Of the GW-deployed veterans, 69.0% scored greater than the cut-off for less than optimal performance (i.e., 48–50), while 78.9% of the Germany-deployed veterans scored in this range. Additionally, there was no significant difference between the number of participants who scored <47 points on the TOMM in the two cohorts (GW-deployed $n = 18$, 31.0%; Germany-deployed $n = 4$, 21.1%; $X^2 = 0.699$, $p = .403$).

Table IV presents results for the combined sample of GW-deployed and the Germany-deployed GW-era veterans. Univariate regression analyses, controlling for age, education, WAIS-R Information age-scaled score, deployment status, and PTSD symptomatology showed a significant relationship between performance on the TOMM and neuropsychological test scores on tasks assessing attention, executive system functions, and memory. Results revealed that veterans in the combined sample who obtained lower scores on the TOMM demonstrated significantly poorer performance on the Trail-making Test

Table I. Descriptive Characteristics and Comparisons (Unweighted) Between High and Low TOMM Scores: GW-Deployed Veterans

	TOMM performance groups		
	Low score (range 38–47)	High score (range 48–50)	
	($n = 18$)	($n = 40$)	Between group p value
Demographic variables			
Age in years (*SD*)	36.1 (9.3)	35.6 (9.8)	.858
Education in years (*SD*)	13.7 (1.8)	14.1 (2.4)	.464
WAIS-R Information Age-Scaled Score (*SD*)	9.1 (3.0)	10.0 (2.1)	.173
Test of Memory Malingering (*SD*)	44.7 (2.9)	49.4 (0.77)	.000**
% Female	44.4	38.5	.669
% Non-Caucasian	11.1	18.9	.463
% Married	44.4	52.5	.570
% Unemployed	11.1	0	.142
% Repeated grade in school	22.2	21.1	.921
% Service in Vietnam	11.1	10.5	.947
% Currently taking medication	0	2.5	.499
% Seeking disability rating	11.1	10.8	.973
% Received anthrax vaccine	0	25.0	.180
% Reported CBW exposure	42.9	26.9	.305
Medical/psychiatric diagnoses			
% History of closed head injury	16.7	10.5	.516
% History of alcohol abuse/problems	5.9	5.7	.981
% History of diabetes	0	2.6	.487
% History of seizure disorder	5.6	0	.143
% History of hypertension	11.1	7.9	.693
% Current diagnosis of depression (SCID)	5.6	0.0	.133
% Lifetime diagnosis of depression (SCID)	33.3	15.0	.111
% Current diagnosis of PTSD (CAPS)	5.6	2.5	.528
% Lifetime diagnosis of PTSD (CAPS)	16.7	2.5	.084
Body system symptoms			
Neurological symptoms (*SD*)	3.1 (3.0)	2.0 (1.9)	.111
Neuropsychological symptoms (*SD*)	5.2 (5.8)	4.2 (4.8)	.483
Psychological symptoms (*SD*)	3.6 (3.2)	2.2 (2.7)	.088
Pulmonary symptoms (*SD*)	2.1 (2.1)	1.2 (2.1)	.164
Gastrointestinal symptoms (*SD*)	3.9 (3.9)	2.7 (2.8)	.192
Genitourinary symptoms (*SD*)	1.2 (2.2)	0.5 (1.1)	.162
Musculoskeletal symptoms (*SD*)	3.5 (3.7)	3.5 (3.5)	.978
Cardiac symptoms (*SD*)	1.9 (2.5)	0.6 (1.7)	.034*

Notes. The t test was used for comparisons of differences in mean scores for continuous variables: χ^2 statistic was used for comparison of differences in proportions for categorical variables. *SD* = standard deviation; CBW = chemical biological warfare agents; PTSD = posttraumatic stress disorder; CAPS = Clinician Administered PTSD Scale; SCID = Structured Clinical Interview for *DSM-III-R*.
*$p < .05$. **$p < .01$.

(TMT; errors), WCST (number of correct sorts), WMS-R Verbal Paired Associate Learning (total immediate recall, immediate recall of difficult items), WMS Visual Reproduction (total copy score, total immediate recall, total delayed recall), and CVLT (cued long delay recall). No statistically significant differences in most demographic characteristics, medical/psychiatric diagnoses, and health symptoms were evident between low and high groups in the combined sample. However, those who scored lower on the TOMM demonstrated a higher rate of lifetime PTSD (% Lifetime diagnosis of PTSD–CAPS: Low 13.6%, High 1.8%, $p = .035$) and endorsed a greater number of cardiac symptoms (Low mean = 1.6, SD = 2.4; High mean = 0.6, SD = 1.5, $p = .029$).

DISCUSSION

An investigation of the relationship between scores on a task assessing motivation to perform well and neuropsychological test performance suggests that the majority of GW-era veterans who participated in the current study were well motivated during neuropsychological testing. Findings show that only a small subset of participants did not perform optimally, or to the best of their ability,

Table II. Relationship Between TOMM Performance and Neuropsychological Performance in Gulf-Deployed Veterans[a]

Tests organized by functional domain	*n*	MANCOVA[b] *p* value	TOMM performance groups adjusted mean (*SE*) Low score (range 48–50) (*n* = 18)	High score (range 38–47) (*n* = 38)	Univariate *F*(1, 52)	*P* value
Attention and executive functions						
Wisconsin Card Sorting Test						
Number of correct sorts	56	.039*	3.5 (0.22)	4.2 (0.15)	6.4	.015*
Memory						
WMS-R Verbal Paired Associate Learning						
Immediate recall: Total score	56	.001*	15.2(0.67)	18.5(0.46)	16.3	.000**
California Verbal Learning Test						
Long delay cued recall, number correct	56	.039*	12.3 (0.53)	13.8 (0.36)	4.9	.030*

Notes. PTSD = posttraumatic stress disorder. WAIS-R = Wechsler Adult Intelligence Scale – Revised; CAPS = Clinician Administered PTSD Scale; WMS = Wechsler Memory Scale; WMS-R = Wechsler Memory Scale – Revised.

[a] Analyses controlled for age and years of education.

[b] Scales administered and not found to differ by level of motivation were WMS-R Verbal PAL (easy items immediate recall, easy items delayed recall); California Verbal Learning Test (Trials 1–5: total perseverations, intrusions; number correct recognition); Finger Tapping (dominant 5 trial mean, nondominant 5 trial mean); Purdue Pegboard (dominant correct, nondominant correct, extra trials); Paced Auditory Serial Addition Test (Trials 1–4); Wisconsin Card Sorting Test (number of sorts, number of errors).

*$p < .05$. **$p < .01$.

on the TOMM and that rates of suboptimal performance were no different in GW-deployed veterans than in Germany-deployed GW-era veterans. Consistent with expectations, high rates of motivational disorders were *not* evident in GW-deployed veterans, and few participants performed at a level that would raise the question of possible purposeful failure of test items.

Although most participants scored above the designated cut-off on the TOMM, a range of performance scores was evident. Importantly, the range of scores observed on the TOMM was sufficient to demonstrate a significant relationship between TOMM score and scores on neuropsychological tests assessing attention, executive system functions, and memory. Results demonstrated

Table III. Comparison of TOMM Scores in Gulf-Deployed and Germany-Deployed GW-Era Veterans

Obtained TOMM scores in Descending Order	Gulf-deployed Frequency	Gulf-deployed Cumulative %	Germany-deployed Frequency	Germany-deployed Cumulative %
50	21	36.2	7	36.8
49	12	56.9	6	68.4
48	7	69.0	2	78.9
47	6	79.3	0	78.9
46	4	86.2	0	78.9
45	3	91.4	2	89.5
44	1	93.1	1	94.7
43	1	94.8	1	100.0
40	1	96.6		
39	1	98.3		
38	1	100.0		
n	58		19	
Mean (*SD*)	47.9 (2.75)		48.3 (2.3)	
Range	38–50		43–50	
t value	0.251			
p value	0.618			

Table IV. Relationship Between TOMM Performance and Neuropsychological Performance in Combined Gulf-Deployed and Germany-Deployed Sample[a]

			TOMM performance groups adjusted mean (*SE*)			
		MANCOVA[b]	Low score (range 38–47)	High score (range 48–50)	Univariate	
Tests organized by functional domain	*n*	*p* value	(*n* = 22)	(*n* = 55)	*F* (1, 67)	*P* value
Attention and executive functions						
Trail-making tests						
Trails B-errors	74	.002**	0.65 (0.14)	0.21 (0.09)	6.9	.010*
Trails, total errors	74	.008**	0.81 (0.15)	0.35 (0.10)	6.2	.015*
Wisconsin Card Sorting Test						
Number of correct sorts	74	.032*	3.48 (0.24)	4.08 (0.15)	5.0	.029*
Visuospatial abilities						
WMS visual reproductions						
Total copy score	73	.006**	12.20 (0.22)	12.80 (0.14)	4.9	.030*
Memory						
WMS-R Verbal Paired Associate Learning						
Immediate recall: Total score	74	.020*	15.34 (0.68)	18.07 (0.44)	11.1	.001**
Immediate recall: Difficult items	74	.030*	4.93 (0.50)	6.92 (0.32)	10.9	.001**
WMS visual reproductions						
Immediate recall: Total score	73	.006**	9.31 (0.43)	10.70 (0.28)	7.2	.009**
Delayed recall: Total score	73	.006**	8.39 (0.48)	9.91 (0.31)	7.0	.010**
California Verbal Learning Test						
Long delay cued recall, number correct	74	.023*	12.02 (0.50)	13.28 (0.32)	4.4	.040*

Notes. PTSD = posttraumatic stress disorder; GW = Gulf War deployed, WAIS-R = Wechsler Adult Intelligence Scale – Revised; CAPS = Clinician Administered PTSD Scale; WMS = Wechsler Memory Scale; WMS-R = Wechsler Memory Scale – Revised.

[a] Analyses controlled for age, education, WAIS-R: Information age-scaled score, deployment status, and PTSD severity.

[b] Scales administered and not found to differ by level of motivation were: WMS-R Verbal PAL (easy items immediate recall, easy items delayed recall); California Verbal Learning Test (Trials 1–5: total perseverations, intrusions; number correct recognition); Finger Tapping (dominant 5 trial mean, nondominant 5 trial mean); Purdue Pegboard (dominant correct, nondominant correct, extra trials); Paced Auditory Serial Addition Test (Trials 1–4); Wisconsin Card Sorting Test (number of sorts, number of errors).

*$p < .05$. **$p < .01$.

that lower scores on the TOMM were significantly associated with lower scores on cognitive tests. The findings highlight the importance of considering motivation as a potential contributing factor when conducting scientific study of this kind.

The TOMM was designed specifically to assess memory malingering (Tombaugh, 1996). Therefore, a significant relationship was expected between motivation to perform well and scores on tests assessing memory. Current findings confirmed these expected relationships. Gulf-deployed veterans who scored lower on the TOMM also scored lower on initial acquisition of verbal material (WMS-R Verbal Paired Associate Learning: immediate recall total) and on delayed retrieval of verbal material (CVLT: cued long delayed recall). Additional findings were evident in the larger, combined sample of GW-era veterans (GW-deployed and Germany-deployed). In the combined sample, those who scored lower on the TOMM also scored lower on initial acquisition of visual material (WMS Visual Reproductions: total immediate recall) and on delayed retrieval of visual material (WMS Visual Reproductions: total delayed recall). Overall, these findings suggest that level of motivation to perform optimally had a significant impact on memory test scores.

In addition to the lower scores on standard memory measures, the combined sample of GW-deployed and Germany-deployed GW-era veterans demonstrated a pattern of inconsistent or variable performance within and between tasks assessing memory abilities. For example, veterans with lower TOMM scores had lower scores on learning of difficult verbal paired associates than on learning of easy paired associates. However, veterans with lower scores on the TOMM demonstrated the *opposite* pattern of performance on the CVLT. On this task, participants with lower TOMM scores had lower scores on the easier cued delayed recall of the word list but did not have lower scores on the harder uncued delayed recall condition. Such variability in test performance is suggestive of limited effort or

motivation to perform well on testing (Tombaugh, 1996; White & Rose, 1996). The current findings suggest that level of motivation had a significant impact on the consistency of memory performance between and within tasks.

In addition to the expected relationship between level of TOMM performance and memory scores, veterans with lower scores on the TOMM earned lower scores on two moderately difficult attention and executive system tasks. Gulf-deployed veterans with lower scores on the TOMM completed fewer sorts on the Wisconsin Card Sorting Test. In the combined GW-era sample, those with lower TOMM scores also made more errors on Trail-making Test Part B. In contrast, lower scores on the TOMM were not associated with lower scores on simple attention and cognitive tracking tasks, such as on digit span performance (Forward and Backward) and Trail-making Test Part A. This finding is similar to that of Binder (1993), who reported that difficult items can be more sensitive than easy items in detecting degree of motivation to perform well. Increased sensitivity of difficult items is also consistent with Hiscock and Hiscock's notion (Hiscock & Hiscock, 1989) that tasks with graduated difficulty may be more sensitive to suboptimal effort or purposeful failure than simple tasks with one level of difficulty. As suggested by Binder (1993), poor motivation on difficult items may be attributed to the performance expectations, which are typically lower on harder items.

Results are consistent in several ways to those obtained by Binder and colleagues (Anger et al., 1999; Binder et al., 2001). Anger et al. (1999) found that a subgroup of GW-deployed veterans with health complaints demonstrated poorer performance on a forced-choice test of motivation, attention, and memory (the Oregon Dual Task Procedure, ODTP). A similar pattern of results was found in GW-deployed veterans demonstrating chronic fatigue syndrome (CFS; Binder et al., 2001). None of the participants described in these reports met criteria for poor motivation (correct identification of <80% of items). However, a subgroup of participants exhibited longer latencies and identified significantly fewer correct responses on the ODTP (Binder, 1993; Binder & Willis, 1991). Anger et al. (1999) also reported that GW-deployed veterans with slow performance on the ODTP obtained lower scores on other neuropsychological tests, including reaction time, symbol-digit latency, digit span forward, and digit span backward.

Interpretation of the current results, which suggest that level of motivation significantly affected performance on selected neuropsychological tests, involves many factors. Variability in test performance, such as diminished performance on more difficult items, may indicate lack of effort or may be associated with mood disorders and psychiatric illness (Binder, 1993; Tombaugh, 1996). In the current sample, participants who scored lower on the TOMM were not characterized by higher rates of current PTSD, current depression, or lifetime depression. However, in the combined sample of GW-era veterans, those who scored lower on the TOMM were found to show a significantly higher rate of lifetime PTSD and significantly more self-reported cardiac related symptoms. A question for further study is why a history of PTSD may have had a negative impact on current symptom presentation and optimal performance on a test such as the TOMM. The finding that cardiovascular symptoms were elevated in these veterans may be of further interest given that cardiovascular arousal has been reported to be elevated in patients with PTSD (Gerardi, Keane, Cahoon, & Klauminzer, 1994).

Although the TOMM score can be used to signal possible false or exaggerated symptoms on neuropsychological testing, a low score on the TOMM does not confirm a diagnosis of malingering (Tombaugh, 1996). The capacity to assess intention and motivation is essential for differentiating purposeful test failure from factitious disorder, somatoform disorder, conversion disorder, anxiety disorder, and depression as defined by the *DSM-IV* (1994).

In conclusion, the current study provides evidence to support the need to assess capacity to perform optimally on cognitive tasks through the use of simple tests that virtually any participant can perform at perfect or near-perfect levels, such as the TOMM. Participants in this study with lower scores on the TOMM obtained lower scores on a range of tests assessing attention, executive abilities, and memory. Hence, level of effort is considered one of many possible factors contributing to patterns of neuropsychological performance in GW veterans. As with all between-group comparisons, findings are interpreted cautiously and cannot be applied meaningfully to any individual case. Results suggest that veterans did not differ significantly on most demographic, health symptom, and psychiatric variables, but those with lower TOMM scores exhibited a higher rate of lifetime PTSD and elevated self-reported cardiac symptoms. How prior traumatic events affect current symptom presentation, motivation to perform well on testing, and perceptions and response to external incentives are important questions relevant not only to the GW-era veteran population but to future veteran and nonveteran populations as well.

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Neuropsychological Performance in Gulf War Era Veterans: Traumatic Stress Symptomatology and Exposure to Chemical–Biological Warfare Agents

Karen Lindem,[1,2,3] Timothy Heeren,[1,4] Roberta F. White,[1,2,3,5,6,7,12] Susan P. Proctor,[1,3,6] Maxine Krengel,[1,2,3] Jennifer Vasterling,[8,9] Patricia B. Sutker,[9,10] Jessica Wolfe,[1,2,3,5,11] and Terence M. Keane[1,2,5,11]

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Because complaints of diminished concentration and memory are among the most common health symptoms reported by Gulf War (GW) veterans with unexplained illnesses, this study investigated neuropsychological functions among GW veterans and controls. Relationships between neuropsychological performance, severity of posttraumatic stress disorder (PTSD) symptomatology, and exposure to chemical–biological warfare agents (CBW) were assessed. Participants were 225 veterans recruited from three cohorts: GW-deployed veterans from Ft. Devens, MA ($n = 141$) and New Orleans, LA ($n = 37$), and Germany-deployed veterans from a Maine National Guard unit ($n = 47$). A comprehensive evaluation was completed. Severity of subclinical PTSD symptomatology was significantly related to scores on specific neuropsychological tests. PTSD symptom severity in GW-deployed veterans was found to be greater and associated with a broader range of neuropsychological deficits than in Germany-deployed veterans. PTSD severity was associated with lower performance on a range of neuropsychological tasks, whereas CBW exposure contributed to performance deficits on specific cognitive tasks.

KEY WORDS: Gulf War syndrome; posttraumatic stress disorder; chemical-biological warfare agents; anxiety disorders; neuropsychological tests.

[1]Boston Environmental Hazards Center, VA Boston Healthcare System, Boston, Massachusetts.
[2]Psychology Department, VA Boston Healthcare System Medical Center, Boston, Massachusetts.
[3]Department of Neurology, Boston University School of Medicine, Boston, Massachusetts.
[4]Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston, Massachusetts.
[5]Department of Psychology, Boston University, Boston, Massachusetts.
[6]Department of Environmental Health, Boston University School of Public Health, Boston, Massachusetts.
[7]University of Southern Denmark, Odense, Denmark.
[8]VA Medical Center, New Orleans, Louisiana.
[9]School of Medicine (Psychiatry and Neurology), Tulane University, New Orleans, Louisiana.
[10]Texas Tech University Health Sciences Center, Lubbock, Texas.
[11]Department of Psychiatry, Boston University School of Medicine, Boston, Massachusetts.
[12]To whom correspondence should be addressed at Boston Environmental Hazards Center, VA Boston Healthcare System Medical Center, 150 South Huntington Avenue (116B-4), Boston, Massachusetts 02130; e-mail: rwhite@bu.edu.

Since their return from the Gulf arena in 1991, Gulf War (GW)-deployed military personnel have continued to report a constellation of health symptoms, including problems with memory and concentration, insomnia, fatigue, headaches, joint and muscle pain, and gastrointestinal disturbance (Persian Gulf Veterans Coordinating Board, 1995; Presidential Advisory Committee, 1996). The etiology of these health problems remains largely undefined, as symptoms do not cluster into a single known or easily understandable disease process (Persian Gulf Veterans Coordinating Board, 1995). The impact of several factors, including psychological distress (e.g., posttraumatic stress disorder [PTSD]) and adverse environmental conditions (e.g., exposure to biochemical warfare agents or pesticides) have been proposed as contributing to unexplained illness presentation in Gulf-deployed GW-era veterans (Haley, 1997, 1998; Landrigan, Lashof, & Hamburg, 1998; Wolfe, Proctor, White, & Friedman, 1998; White et al., 2001).

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measures as sensitive indicators of CNS integrity. The two primary goals of the study were (1) to evaluate the relationships between subclinical PTSD symptomatology and neuropsychological performance, and (2) to assess the relative contributions of PTSD severity and exposure to CBW agents on neuropsychological performance in GW-deployed veterans.

METHODS

This study was part of a larger center project investigating outcome measures in GW veterans upon their return from the Gulf, and data were collected between 1994 and 1996. The overall project had several goals, including assessment of health symptoms, psychiatric status, and neuropsychological status in GW-era veterans deployed to the Gulf and to Germany.

Participants and Recruitment

Participants in this study were 225 troops from three cohorts of GW and GW-era veterans. Veterans deployed to the Gulf were recruited from a group that returned from the Gulf to Ft. Devens, MA ($n = 141$) and to New Orleans, LA ($n = 37$). Veterans deployed to Germany were recruited from a National Guard unit in Maine ($n = 47$). Data on demographic and health variables were collected, including age, highest educational level attained, race, gender, marital status, employment status, medication use, prior military service, and disability status.

Devens Cohort

A detailed description of recruitment and assessment methods of the Devens cohort has been provided by Proctor et al. (1998). The original cohort consisted of 2,949 U.S. GW veterans (2,709 men, 240 women) who were deployed through Fort Devens, MA. This cohort of GW-deployed veterans was assessed at several time points between 1991 and 1996. Initial surveys (Time 1) were completed within 5 days of returning to this country, between April and July of 1991. This initial survey assessed demographics, self-reported combat exposure, and psychological well being. Veterans were surveyed a second time between 1992 and 1994 (Time 2), approximately 18–24 months after initial testing. Overall response rate was 79%. Over 2,000 veterans (2,121 men and 194 women) completed the Time 2 assessment, which included all measures from Time 1 and questions regarding work status, family and social functioning, health status, health service use, and intervening life stressors.

A third evaluation of a subsample of the Devens cohort was completed between 1994 and 1996 (Time 3). This included neuropsychological evaluation, self-reported environmental exposure assessment and health history, review of military and nonmilitary life stressors, and psychodiagnostic assessment of Axis I disorders. The participant selection for the Time 3 studies was carried out by random stratified sampling based on unit designation, health symptom reporting, and gender (Proctor et al., 1998). Random sampling yielded 353 veterans, of whom 261 (73.9%) were contacted by phone, 88 (24.9%) were unable to be reached, and 4 (1.1%) were deceased. Of the 261 veterans contacted, 220 (84.3%) participated in at least one aspect of the Time 3 assessment. A number of the selected sample veterans resided outside commuting distance to the testing site, thereby limiting the number who completed all assessment measures to 141. Data from the 141 veterans who completed all evaluations are included in this study.

New Orleans Cohort

The original New Orleans cohort consisted of 928 Active, Reserve, and National Guard troops representing U.S. Army, Navy, Marine, and Air Force personnel deployed to the Gulf. An initial survey was conducted in 1991, a few months after troops had returned to the United States. A stratified random sampling procedure similar to that used for the Devens cohort was used for recruitment. A random sample of 194 veterans was identified, 125 (64.4%) veterans were contacted by telephone, 91 were scheduled for evaluation, 73 (58% of those contacted) were seen for assessment, and 51 veterans participated in neuropsychological testing and psychiatric diagnostic interviews. Of these, 37 veterans completed the Clinician Administered PTSD Scale (CAPS, see later). Data from the 37 veterans with full neuropsychological and PTSD evaluations were included in this study.

Germany-Deployed GW-Era Cohort

The Germany cohort is drawn from an air ambulance unit that was mobilized during the GW and deployed to Germany. This unit was chosen as a comparison group because it experienced the stress and dislocation of deployment but was not exposed to environmental and combat-related events and conditions specific to the GW theatre. The unit, which aided German civilian evacuation and transport missions, served in Germany between December 1990 and August 1991. Fifty participants (85% of those who could be located; 51% of the deployed unit) were tested in the spring of 1995. Forty-seven participants

questionnaire asking them to record if they had experienced any of eight environmental exposures specific to the Gulf arena (see Proctor et al., 1998). These included exposure to pyridostigmine bromide (PB, antinerve gas pills), pesticides, debris from SCUDs, smoke from burning oil wells, vehicle exhaust, smoke from tent heaters, smoke from burning human waste, and chemical or biological warfare agents. The eight exposure variables were evaluated using a binary scale (0 = *no exposure*, 1 = *exposed*).

Combat Exposure

Veterans were asked to report exposure to war-zone related stressors on the Expanded Combat Exposure Scale (CES; Rosenheck et al., 1991). The CES is a 34-item scale designed to assess presence and frequency of prominent war zone stressors. The Expanded Scale was redesigned to include additional war zone stressors specific to the GW. These additional items included lack of communication among units, exposure to poison gas or germ warfare, and placement on formal alert for chemical or biological warfare attack.

Health Symptoms

Veterans completed the Expanded Health Symptom Checklist (HSC) as described by Proctor et al. (1998). A 20-item checklist of health symptoms (Bartone, Ursano, Wright, & Ingraham, 1989) was administered initially in the 1992/1993 survey. Subsequently, an expanded list of 52 items was developed to assess current health complaints and change in the original 20 items over time. The HSC determined how often the 52 health symptoms were experienced over the 30 days prior to answering HSC items. Symptoms from nine body systems were assessed (cardiac, pulmonary, dermatological, gastrointestinal, genitourinary, musculoskeletal, neurological, neuropsychological, and psychological). Responses were recorded on a 5-point scale (0 = *never*, 1 = *once or twice in all*, 2 = *about once/week*, 3 = *several times/week*, 4 = *almost every day*).

Data Analyses

Between-group comparisons of health complaints, environmental exposures, and neuropsychological performance differences between the Devens, New Orleans, and Germany cohorts have been presented previously by Proctor et al. (1998) and White et al. (2001). Between-group comparisons of demographic variables, health-related conditions, and health symptoms specific to the GW-deployed veterans ($n = 178$) from Devens and New Orleans and to the Germany-deployed ($n = 47$) veterans who completed full PTSD evaluations and neuropsychological assessment are presented in this paper. The t test was used for comparisons of differences in mean scores for continuous variables. Since standard deviations varied dramatically across groups for some study variables, variances were first compared between groups through an F test. Differences in means were tested either through the equal variance version or the separate variance version of the t test, depending on the significance of the difference in variances. The chi-square statistic was used for comparisons of differences in proportions for categorical variables.

Partial correlation analyses were performed to investigate whether a relationship was evident between severity of PTSD symptom reporting and neuropsychological performance in GW-deployed and Germany-deployed veterans as a combined group. Analyses controlled for age, education, WAIS-R Information age-scaled score, deployment status (GW or Germany), depression at the time of assessment as measured by the SCID, and disability status.

To investigate further relationships between severity of PTSD, CBW exposure, and neuropsychological performance the following analyses were conducted. First, to assess the impact of deployment to the Gulf theatre on the relationship between severity of PTSD symptomatology and neuropsychological performance, partial correlation analyses between PTSD severity and neuropsychological test variables, controlling for age, education, and WAIS-R Information age-scaled score, were conducted separately for veterans deployed to Germany and for those deployed to the Gulf. Second, the relationship between severity of PTSD symptomatology and neuropsychological performance in GW-deployed veterans was investigated in participants who reported exposure to CBW agents and in participants who reported no exposure to such agents. Partial correlation analyses comparing PTSD severity and neuropsychological performance, controlling for age, education, WAIS-R Information age-scaled score, deployment status, depression, and disability status, were performed separately for GW-deployed veterans who reported exposure to CBW agents while in the Gulf and GW-deployed veterans who reported no exposure to CBW agents while in the Gulf. Finally, regression analyses were performed to determine the relative contribution of PTSD severity and exposure to CBW on neuropsychological performance across all cognitive domains, controlling for age, education, and WAIS-R Information age scaled score.

Table II. Reported Health-Related Conditions and Symptoms, Comparing (Unweighted) Study Cohorts

	GW-deployed ($n = 178$)	Germany-deployed ($n = 47$)	Significance
Health-related conditions			
% Currently taking medication	4.7	0.0	*ns*
% Seeking disability rating/upgrade	9.3	0.0	.036*
% Received anthrax vaccine	20.3	—	—
% Reported CBW exposure	22.6	—	—
Medical/psychiatric conditions			
% History of closed head injury	8.6	0.0	.041*
% History of alcohol abuse/problems	9.0	7.1	*ns*
% History of diabetes	2.3	0.0	*ns*
% History of seizure disorder	1.7	0.0	*ns*
% History of cancer/leukemia	0.6	4.4	.048*
% History of hypertension	9.2	4.4	*ns*
% Current diagnosis of depression (SCID)	5.1	0.0	*ns*
% Lifetime diagnosis of depression (SCID)	20.5	4.3	.005**
% Current diagnosis of PTSD (CAPS)	2.8	0.0	*ns*
% Lifetime diagnosis of PTSD (CAPS)	7.3	0.0	*ns*
CAPS severity score (*SD*)	12.6 (18.7)	2.2 (4.6)	.001**
Body system symptoms			
Neurological symptoms	2.3 (2.3)	0.82 (1.3)	.000**
Neuropsychologicl symptoms	4.4 (4.7)	1.3 (2.4)	.000**
Psychological symptoms	10.2 (10.3)	3.2 (5.0)	.000**
Pulmonary symptoms	1.4 (1.8)	0.61 (.99)	.000**
Gastrointestinal symptoms	2.5 (3.0)	0.51 (1.4)	.000**
Genitourinary symptoms	0.65 (1.5)	0.31 (0.8)	.050*
Musculoskeletal symptoms	3.4 (3.5)	1.9 (2.3)	.001**
Cardiac symptoms	1.0 (2.0)	0.24 (0.8)	.000**
Dermatological	0.72 (1.3)	0.09 (0.36)	.000**

Note. The *t* test was used for comparisons of differences in mean scores for continuous variables. Chi-square statistic was used for comparison of differences in proportions for categorical variables. SCID = Structured Clinical Interview. for DSM-III-R Diagnoses, CAPS = Clinician Administered PTSD Scale.
ns = not significant, $p > .05$.
*$p < .05$. **$p < .01$.

Pegboard: dominant hand, nondominant hand, extra trials), verbal learning (CVLT: learning trials, clustering strategies, short delayed recall), visual memory (WMS visual reproduction: recognition total score) and on all mood subscales except Vigor (POMS: tension, depression, anger, fatigue, and confusion). Between-group comparisons of neuropsychological performance among the GW-deployed and Germany-deployed cohorts are not

Table III. Comparison of Severity of PTSD Symptomatology Between GW-Deployed and Germany-Deployed Veterans and Between GW-Deployed Veterans with CBW Exposure and GW-Deployed Veteran with no CBW Exposure

	GW-deployed ($n = 178$)	Germany-deployed ($n = 47$)	*t*	*p* value
CAPS severity score, mean (*SD*)	12.6 (18.7)	2.2 (4.6)	−6.7	.000**
CAPS severity score, range	0–109	0–21		
	GW-deployed with CBW exposure ($n = 30$)	GW-deployed with no CBW exposure ($n = 103$)		
CAPS severity score, mean (*SD*)	28.2 (30.0)	7.3 (10.2)	−3.8	.001**
CAPS severity score, range	0–109	0–59		

Note. t test was used for comparisons of differences in mean scores for continuous variables.
**$p < .01$.

Table V. Correlations Between Severity of PTSD Symptoms and Neuropsychological Performance in GW-Deployed Veterans Controlling for Age, Education, and WAIS-R Information Age-Scaled Score (GW-Deployed Only)

Tests organized by functional domain	*n*	Beta-weights for CAPS (standardized regression coefficient)	*p* value for factor weight	Partial R^2 for CAPS in model
General intellectual abilities				
WAIS-R Information[a]	172			
Age-scaled score		−.1630	.032*	.0266
Raw score		−.2063	.006**	.0425
Attention and executive functions				
Continuous performance test	158			
Total mean reaction time		.1806	.022*	.0326
Total standard deviation		.2250	.004**	.0506
Total median reaction time		.1670	.035*	.0279
Motor/psychomotor function				
Finger tapping test	171			
Dominant hand		−.2236	.003**	.0500
Nondominant hand		−.1782	.019*	.0318
Purdue Pegboard	171			
Dominant hand		−.1698	.025*	.0288
Nondominant hand		−.1703	.025*	.0290
Memory				
California verbal learning test	171			
Total number correct, Trials 1–5	169	−.2270	.003**	.0515
Total number of clusters, Trials 1–5	169	−.1830	.017*	.0335
Tuesday list—number correct		−.1552	.041*	.0241
Tuesday list—number of clusters		−.1962	.010**	.0385
Short delay recall—number of clusters		−.1518	.046*	.0230
Long delay, cued recall—number of perseverations		.1504	.048*	.0226
Number correct on recognition		−.1591	.037*	.0253
Visual reproduction	169			
Recognition total		−.3230	.000**	.1043
Mood				
Profile of mood states	171			
Tension, *t* score		.3751	.000**	.1407
Depression, *t* score		.4465	.000**	.1994
Anger, *t* score		.3118	.000**	.0972
Fatigue, *t* score		.3275	.000**	.1073
Confusion, *t* score		.4450	.000**	.1980
Vigor, *t* score		−.2413	.001**	.0582

Note. PTSD = posttraumatic stress disorder. WAIS-R = Wechsler Adult Intelligence Scale – Revised. GW = Gulf War. CAPS = Clinician Administered PTSD Scale. WMS = Wechsler Memory Scale.

[a] Covariates for WAIS-R Information scores included age, education.

*$p < .05$. **$p < .01$.

reported CBW exposure revealed a significant relationship between severity of PTSD symptomatology and neuropsychological performance on variables assessing sustained attention (CPT: mean reaction time, median reaction time), motor speed (finger tapping: dominant hand, nondominant hand), and motor coordination (Purdue Pegboard: dominant hand, nondominant hand). For GW veterans who did not report exposure to CBW agents while in the Gulf (see Table VIII), partial correlation analyses showed a significant relationship between severity of PTSD symptomatology and neuropsychological performance on variables assessing cognitive tracking (Trails A and B: number of errors; PASAT: Trial 4), motor speed (finger tapping: dominant hand, nondominant hand), motor coordination (Purdue Pegboard: extra trials), and mood (POMS: tension, anger, and confusion).

Regression analyses were used to investigate the relative contribution of PTSD severity and CBW exposure to neuropsychological performance in GW-deployed veterans, controlling for age, education, and WAIS-R Information raw score. In Table IX, results from regression analyses are presented, which demonstrate that severity

Table VIII. Correlations Between Severity of PTSD Symptoms and Neuropsychological Performance in GW-Deployed Veterans with no CBW Exposure Controlling for Age, Education, WAIS-R Information Age-Scaled Score, Depression, and Disability (GW w/o CBW Exposure $n = 103$)

Tests organized by functional domain	n	Beta-weights for CAPS (standardized regression coefficient)	p value for factor weight	Partial R^2 for CAPS in model
Attention and executive functions				
Trail Making Test	93			
Trails A, errors		.2250	.028*	.0008
Trials B, errors		−.2126	.039*	.0015
PASAT	90			
Trial 4, number correct		.2425	.020*	.0004
Motor/psychomotor function				
Finger Tapping Test	93			
Dominant hand		−.2289	.026*	.0007
Nondominant hand		−.2848	.005**	.0000
Purdue pegboard	93			
Extra trials		.2519	.014*	.0002
Mood				
Profile of Mood States	93			
Tension, t score		.3062	.003**	.0000
Anger, t score		.2036	.048*	.0023
Confusion, t score		.2496	.015*	.0002

Note. PTSD = posttraumatic stress disorder. CBW = chemical–biological warfare agents. WAIS-R = Wechsler Adult Intelligence Scale – Revised. CAPS = Clinician Administered PTSD Scale PASAT = Paired Auditory Serial Arithmetic Test.
*$p < .05$. **$p < .01$.

military duty. Without doubt, deployment to a war zone is associated with acute and chronic stressor events, ranging from disruption of family and work relationships to combat and death. Specific environmental stressors experienced by GW veterans have been documented, including threat of or actual exposure to chemical warfare agents and exposure to other possibly neurotoxic substances such as smoke from burning waste and burning oil wells, SCUD missile debris, depleted uranium, and antinerve gas pills (Presidential Advisory Committee, 1996; Proctor et al., 1998). Although exposure to such war zone stressors and subsequent stress reactions are subject to individual variability, it is conceivable that reactions to deployment and war zone related stressors were of sufficient intensity and duration to produce chronic physiological and psychological reactions in some GW-deployed veterans. At the extreme end of the continuum, cases of current PTSD were identified in 46 and 48% of GW-deployed quartermaster troops who performed graves registration duties in the GW (Sutker, Uddo, Brailey, Allain, & Errera, 1994; Sutker, Uddo, Brailey, Vasterling, & Errera, 1994). Given the horrific and gruesome GW–war-zone events experienced by these troops, it is not surprising that symptoms were sufficiently severe to meet full classification criteria in almost half of the GW-deployed quartermaster troops.

Representing one end of the continuum, traditional use of assessment tools for diagnosing PTSD involves defining "cases," and only those individuals with symptom severity scores meeting a given cutoff score are identified. In such instances, a clinical diagnosis of PTSD is based on specific criteria (Diagnostic and Statistical Manual of Mental Disorder, 4th ed.; American Psychiatric Association, 1994), with characteristic symptoms including persistent reexperiencing of the traumatic event (e.g., recollections, distressing dreams, or flashbacks), avoidance of reminders of the event, and increased arousal (e.g., difficulty sleeping and concentrating). Although symptom severity of noncases may not exceed diagnostic criteria at the time of assessment, it can be argued that noncases may still be symptomatic or may experience health consequences, as was evident in the current samples of GW-era veterans.

Results from this study are based on samples of GW-era veterans who demonstrated a low incidence of diagnosed PTSD at the time of assessment, approximately 3–4.5 years following return from deployment. Despite the low incidence of clinical PTSD, the range of trauma-related symptoms provided an opportunity to investigate the relationship between subclinical levels of traumatic stress measured on a continuum and neuropsychological test performance in veterans deployed to active combat

The psychomotor findings from this study suggest a relationship between severity of PTSD symptomatology and regulation of motor pathways that aid in planning, executing, and regulating motor speed and coordination. The data indicate that subclinical levels of PTSD were associated with slower motor speed and motor coordination. These findings are consistent with previous research demonstrating slowed motor response speed in patients with diagnosed PTSD (Attias, Bleich, Furman & Zinger, 1996). Present data were also consistent with an expected significant relationship between severity of PTSD symptomatology and reporting of mood complaints. These results raise the possibility that poor performance on tests of attention and memory may reflect mood (Massman, Delis, Butters, Dupont, & Gillin, 1992), such that severity of PTSD symptoms contributed significantly to ability to attend to neuropsychological tasks without distraction, which in turn may have affected performance on other cognitive tasks.

Lower intellectual ability has been identified as a risk factor for PTSD in previous investigations (Macklin et al., 1998; Vasterling et al., 1997, 2002). Performance on tests of overlearned crystallized information, such as the WAIS-R Information subtest, have been shown to be resistant to CNS injury and therefore are frequently used to estimate or control for premorbid intellectual abilities (Lezak, 1995). In the current study, lower scores on a test of general intellectual ability were associated with increased PTSD symptom severity. This study contributes to previous findings that point to a relationship between lower premorbid intellectual ability and the development of PTSD symptoms following exposure to a traumatic event. This appears to hold true for subclinical levels of PTSD as well.

The Germany-deployed cohort was included in the current study to provide an opportunity to investigate the effects of specific environmental stressors associated with military service in the GW era without the possible confounding impact that military deployment in general may have exerted on veterans. Severity of PTSD symptomatology was found in the current study to be significantly lower in veterans deployed to Germany when compared to veterans deployed to the Gulf. Although the range of PTSD symptom scores was limited in veterans deployed only as far as Germany and fewer subjects were available in this cohort, severity of PTSD symptoms was nonetheless found to be significantly associated with a range of neuropsychological performance difficulties. For veterans deployed to the Gulf, severity of PTSD symptomatology was greater and was associated with a wider range of lowered scores on neuropsychological tests than was evident in veterans deployed only to Germany.

The current analyses, combined with those from previous studies (e.g., Vasterling et al., 1998), suggest that a progression of neuropsychological deficits may be associated with increasing levels of PTSD symptom severity. In this study, mild PTSD symptoms were associated with attentional difficulties and mood complaints. Moderate, but subclinical, PTSD symptomatology was associated with difficulty sustaining attention, slowed motor performance, learning and short-term memory retrieval difficulties, and mood complaints. Clinical levels of PTSD have also been shown in previous studies to be associated additionally with increased difficulty inhibiting intrusive responses across sustained attention and learning tasks (Vasterling et al., 1998). Results suggest that increasing PTSD severity is associated with greater neuropsychological dysfunction.

In the current sample, a small number of veterans reported that they had been exposed to CBW agents while in the Gulf ($n = 30$), while most reported no exposure to such agents ($n = 103$). Severity of PTSD symptomatology differed significantly between the groups, with those reporting CBW exposure also reporting greater severity of PTSD symptomatology. Findings suggest that the relationship between PTSD and neuropsychological performance differed in veterans who reported CBW exposure versus those who did not, primarily on assessment of mood.

The impact of multiple factors such as psychological distress (e.g., PTSD) and adverse environmental conditions (e.g., exposure to biochemical warfare agents or pesticides) on unexplained health problems of GW-deployed veterans continues to generate much debate (Haley, 1997, 1998; Landrigan et al., 1998; Wolfe et al., 1998). The current study is the first to investigate the relative contributions of stress severity and self-reported exposure to biochemical warfare agents specifically on one indicator of health outcome, namely neuropsychological function. Findings suggest that severity of subclinical PTSD contributed to performance on a wider range of neuropsychological tasks than did self-reported exposure to CBW. Severity of subclinical PTSD was significantly associated with poorer performance on tasks assessing general intellectual ability, sustained attention, motor speed, verbal list learning, visual memory multiple choice, and mood. In contrast, exposure to CBW contributed to poorer performance on very specific cognitive tasks, that is, those assessing sustained attention, number of perseverative responses (verbal memory delayed recall), visual memory (delayed recall), and mood measures assessing confusion and fatigue. These results regarding highly specific cognitive findings are consistent with prior studies investigating the effects of neurotoxicants on neuropsychological function (White, 2001).

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Neuropsychological Function in Gulf War Veterans: Relationships to Self-Reported Toxicant Exposures

Roberta F. White, PhD,[1,2,3,4,5,6*] Susan P. Proctor, DSc,[1,3,4] Timothy Heeren, PhD,[1,7] Jessica Wolfe, PhD,[1,2,4,5,8] Maxine Krengel, PhD,[1,2,4] Jennifer Vasterling, PhD,[9,10] Karen Lindem, PhD,[2,4] Kristin J. Heaton, MS,[1] Patricia Sutker, PhD,[9] and David M. Ozonoff, MD, MPH,[1,3,11]

Background *The present study was aimed at (1) exploring evidence of central nervous system (CNS) dysfunction among Gulf War (GW) veterans on neuropsychological tests and (2) examining whether performance on neuropsychological tests was related to specific neurotoxicant exposures experienced in the Gulf.*

Methods *The GW-deployed groups were selected using stratified random sampling methods from two distinct cohorts of GW veterans. A comparison group that had been called up for GW service but deployed to Germany rather than the Gulf also was examined. Neuropsychological function was assessed using a pre-determined battery chosen to include tests known to be highly sensitive to the behavioral effects of the neurotoxicants thought to have been present in the Gulf.*

Results *Self-reported exposures were related to neuropsychological test performance controlling for post-traumatic stress disorder, major depression, and other known covariates of neuropsychological test performance. Results showed that GW-deployed veterans performed more poorly than the Germany-deployed veterans on several specific neuropsychological tests, but after adjustment for multiple comparisons, only the differences in mood complaints remained significant. Within the GW-deployed group, self-reported exposure to chemical warfare agents was associated with poorer performance on cognitive tests involving specific functional domains.*

Conclusions *Results provide evidence that there are subtle differences in CNS function among GW-deployed veterans who report chemical warfare agent exposure while in the GW theater.* Am. J. Ind. Med. 40:42–54, 2001. © *2001 Wiley-Liss, Inc.*

KEY WORDS: neuropsychology, Gulf War veterans, cognitive function, environmental exposures

[1]Boston Environmental Hazards Center, VA Boston Healthcare System, Boston, Massachusetts
[2]VA Boston Healthcare System, Psychology Department, Boston, Massachusetts
[3]Boston University School of Public Health, Department of Environmental Health, Boston, Massachusetts
[4]Boston University School of Medicine, Department of Neurology, Boston, Massachusetts
[5]Boston University, Department of Psychology, Boston, Massachusetts
[6]University of Southern Denmark, Odense, Denmark
[7]Boston University School of Public Health, Department of Epidemiology and Biostatistics, Boston, Massachusetts
[8]Boston University School of Medicine, Department of Psychiatry, Boston, Massachusetts
[9]New Orleans DVAMC, New Orleans, Louisiana
[10]Tulane University, School of Medicine (Psychiatry and Neurology), New Orleans, Louisiana
[11]VA Boston Healthcare System, Medical Service, Boston, Massachusetts
*Correspondence to: Dr. Roberta F. White, Boston Environmental Hazards Center, VA Boston Healthcare System, 150 South Huntington Avenue (116B-4), Boston, MA 02130. E-mail: rwhite@bu.edu

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INTRODUCTION

Military personnel returning from the Gulf War (GW) have reported symptoms that have not only defied diagnosis using known disease entities but also do not appear to occur in a predictable constellation that can be classified as a single syndrome [Persian Gulf Veterans Coordinating Board, 1995; Institute of Medicine, 1996; Iowa Persian Gulf Study Group, 1997; Wegman et al., 1997; Proctor et al., 1998; Wolfe et al., 1998]. However, prominent among complaints reported by a high percentage of several samples of GW veterans are symptoms that suggest dysfunction in the central nervous system (CNS). These include memory loss, concentration problems, headaches, and fatigue.

Military personnel in the Gulf were exposed to a number of chemicals that are known to be neurotoxic, including pesticides, chemical warfare agents, pyridostigmine bromide (anti-nerve gas pills), and combustion by-products produced by the oil well fires [Presidential Advisory Committee on Gulf War Veterans' Illness, 1996]. This raises the question of whether the CNS dysfunction reported by some GW veterans is related to exposure to these neurotoxicants.

A well-established tool for investigating CNS dysfunction following neurotoxicant exposures is neuropsychological test methodology [Anger, 1990; White et al., 1990; White and Proctor, 1992]. Neuropsychological tests are especially useful because they can quantify behavioral deficits in persons with clinically obvious physical evidence of intoxication following exposure as well as detect subtle dysfunction in exposed persons with no obvious clinical disease [Baker and White, 1985]. Subtle CNS dysfunction in persons without clinically obvious disease has been demonstrated since at least the 1970's using this methodology [Hanninen, 1971] and has been labeled "subclinical" [White et al., 1990] or "pre-clinical" [Echeverria et al., 1995] encephalopathy. The detection of subtle CNS dysfunction using neuropsychological methodology is most elegantly demonstrated in prospective group studies in which dose–effect relationships are revealed [e.g., Baker et al., 1984; Grandjean et al., 1997].

Neuropsychological methods can be used to detect subtle residual CNS effects of exposure that persist for long periods of time after the exposure occurred. For example, mood, neurophysiological, and motor deficits were found 6 months after treatment for sarin poisioning [Murata et al., 1997; Yokoyama et al., 1998]. Chronic exposure to solvents [White and Proctor, 1997] and pesticides [Rosenstock et al., 1991] have also been associated with persistent neuropsychological deficit in the absence of diagnosed CNS dysfunction at the time of exposure.

We approached the question of whether GW veterans may have sustained CNS damage (due to toxicant exposure or some other deployment-related experience) using neuropsychological methodology. To date, little research has been published that examines neuropsychological function in this population [Axelrod and Milner, 1997; Goldstein et al., 1996; Hom et al., 1997] The research that has emerged so far has had serious limitations. Some problems with the studies include small sample sizes and subject selection bias [Axelrod and Milner, 1997; Goldstein et al., 1996; Hom et al., 1997]. These studies also tend to lack appropriate control populations for comparison purposes. One study [Axelrod and Milner, 1997], with no control group, compared GW veterans' performance to various normative values, some of which were not specific to the veteran population. Another study used a comparison group of unclear comparability to the veterans (i.e., local community members, [Goldstein et al., 1996]). A third found pervasive differences between the target population and controls but differences in performance extended to tests that are known to be robust in the face of brain insults (i.e., Wechsler Intelligence summary indices, [Hom et al., 1997]), thus suggesting that there was a significant difference in underlying cognitive function between the GW group and the controls that predated any GW experiences. Another serious problem with the currently published studies is that statistical analyses did not adequately control for the known covariates of neuropsychological test performance (age, gender, education, existence of developmental disorders of learning and attention, and performance on "hold" tests). An especially serious limitation in two studies [Axelrod and Milner, 1997; Hom et al., 1997] was the failure to control for psychopathology or post-traumatic stress disorder (PTSD) status, despite documenting significant indicators of psychopathology in their reports on the psychological data collected on their subjects. This is a matter of concern because Goldstein et al. [1996] found that the minimal cognitive findings in GW veterans disappeared when psychopathological status was entered into the analyses. Similarly, Vasterling et al. [1997], studying PTSD in GW veterans, found that the GW veterans with PTSD had lower scores on tests of crystallized intelligence, suggesting lower premorbid verbal abilities in veterans who developed PTSD. Finally, Sillanpaa et al. [1997] found that neuropsychological findings in GW veterans were attributable to "emotional factors" such as depression and stress.

A well-designed study of behavioral function using a case–control design in which all subjects were GW veterans examined computer-assisted measures of attention and memory while carefully evaluating psychiatric status [Anger et al., 1999]. This study used a liberal case definition of unexplained GW-related illness and concluded that there was evidence of cognitive dysfunction in a subset of the "cases".

None of the studies that have appeared so far has systematically examined relationships between chemical exposures in the Gulf and neuropsychological test performance. Although Hom et al. [1997] claim that the relative

deficits in test performance shown by their GW-deployed group were attributable to pesticide exposure, no examination of exposure–effect relationships was presented in the paper. Furthermore, the "deficits" reported were far more extensive than one would expect in either clinical or subclinical manifestations of pesticide intoxication. The few well-controlled studies of pesticide exposures suggest that exposure-related changes in cognitive function are either minimal [Fiedler et al., 1997] or limited to very few neuropsychological domains, including motor function and perhaps visuospatial skills, attention, and executive function [Rosenstock et al., 1991; Savage et al., 1988; Steenland et al., 1994]. The results, therefore, are inconsistent with the known effects of the exposure invoked to explain the results.

The present study was aimed at (1) exploring the possibility that GW veterans would show evidence of CNS dysfunction on neuropsychological tests and (2) examining whether performance on neuropsychological tests was related to specific chemical exposures experienced in the Gulf.

METHODS

The present study was part of a larger center project (conducted between late 1994 and the spring of 1996) that studied outcomes in GW veterans approximately 4 years after their return from the GW. The Institutional Review Board approved the protocol and informed consent was obtained from each of the 343 subjects who participated (Devens, n = 220; New Orleans, n = 73; Germany, n = 50) in at least one part of the protocol. Because a number of subjects lived outside of commuting distance to either the New England or Louisiana test-sites, only 240 subjects (Devens, n = 142; New Orleans, = 51; Germany, n = 47) completed the in-person neuropsychological testing and psychiatric diagnostic interviews.

Study Population

Three cohorts were studied, two of veterans deployed to the Gulf and one of veterans deployed only as far as Germany. The Gulf-deployed veterans were selected from two larger cohorts via a stratified, random sampling strategy designed to produce an equal representation of these reporting higher and lower symptoms and to oversample for women. The Germany-deployed cohort was a sample of a National Guard unit from Maine. (See [Proctor et al., 1998] for a further description of the subject group and the sampling methodology.)

Devens cohort

The original Devens cohort includes 2,949 US Army Active, Reserve, and National Guard veterans followed since their return to the United States immediately after the war. An initial survey (Spring 1991) was conducted at Ft. Devens, MA, within 5 days of return, before soldiers rejoined their families, and assessed psychological well-being, demographics, and self-reported combat exposure [Wolfe et al., 1992, 1993]. The cohort is largely male (92%), Caucasian (83%), and from the National Guard component (52%). Thus, in some respects, it differs from the troop duty status and ethnic breakdown of the total US Gulf force, which was 17% Reserve and Guard troops, and 68% Caucasian [Department of Defense, 1994]. In Winter 1992/Spring 1993, 2,313 of these veterans (78% response rate) completed a follow-up survey designed to assess longer-term self-reported physical and psychological well-being [Wolfe et al., 1998]. Comparison of respondents and non-respondents for this second survey showed a significantly higher percentage of non-respondents were on active duty (53% vs. 21%, $P < 0.001$) and of African-American background (17% vs. 6%, $P < 0.001$), but they did not differ in sex or education level. For this study, we selected a stratified, random sample of 343 of the respondents who completed the Health Symptom Checklist [HSC] [Bartone et al., 1989] during the 1992/1993 survey. Of these, 220 (85% of those who could be located and contacted; 62% of the total) participated in at least one part of the present study protocol.

New Orleans cohort

The New Orleans cohort consists of 928 Active, Reserve, and National Guard, US Army, Navy, Marine, and Air Force troops deployed to the Gulf. It has also been followed since its return to this country. An initial survey was conducted within 9 months (on average) of their return in 1991 [Brailey et al., 1998]. They were largely male (87%), but had a higher proportion of African–Americans (34%) and included other branches of the service besides Army personnel. The make-up of the New Orleans group also differs to some extent from the overall US GW troop contingent. We selected a stratified, random sample of 194 of the initial respondents who completed the HSC, of which 73 (58% of those who could be located and contacted; 38% of those sampled) participated in at least one part of the study protocol between Summer 1994 and Fall 1995. Budgetary constraints prevented continued recruitment of study subjects past September 1995.

Germany-deployed cohort

A unit from an air ambulance company activated and sent overseas to Germany during the PGW (December 1990–August 1991) was recruited as a comparison group. It consisted of medics, helicopter pilots, flight crews, mechanics, communications specialists, and administrative

support personnel whose intended mission was the handling and transport of wounded US soldiers evacuated from the Gulf. Due to low US casualties, however, the unit assisted German civilian evacuation and transport missions. Fifty subjects (85% of those who could be located and contacted; 51% of the deployed unit) were tested in the Spring of 1995.

Study protocol and measures

The complete study protocol included two types of questionnaires, an environmental interview, a neuropsychological test battery, and psychological diagnostic interviews. The current report focuses on neuropsychological test performance and exposure histories as reported by the participants who completed the questionnaire.

Neuropsychological test battery

The neuropsychological test battery was designed to assess abilities across the following functional domains: general intelligence, attention/executive function, motor ability, visuospatial processing, verbal and visual memory, mood, and motivation. Tests used are listed and described in Table I. The battery required approximately 2 hours to complete and the order of presentation of tasks was the same for all subjects.

Environmental exposures

GW-deployed subjects were asked to record on a questionnaire whether they were exposed to several GW-specific agents, including anti-nerve gas pills, pesticides, debris from Scuds, and smoke from burning oil well fires. Each exposure response was scaled 0–2 (0 = no exposure; 1 = exposed and did not feel sick at the time; 2 = exposed and felt sick at the time). In addition, a specific item from the Expanded Combat Exposure Scale (see below) was used; this item asked the frequency of exposure to poison gas or germ warfare (0 = none, 1 = once, 2 = two or more times), and is referred to as "CW agents" in the analyses. A binary yes/no response (0 = no, 1 or 2 recoded to 1 = yes) was used for each of these exposure variables.

PTSD and war-zone exposures

The clinical diagnosis of PTSD (dichotomous outcome) was determined using the Clinician Administered PTSD Scale (CAPS) [Blake et al., 1990] for all the subjects who completed the neuropsychological testing. The Expanded Combat Exposure Scale (CES) was used to quantify war-related stress exposures. This is a 34-item scale designed to assess the presence and frequency of a range of prominent war-zone stressors. A priori scoring protocols yield two summary scores: the traditional scale (Laufer) score [score range: 0–14; Gallops et al., 1981] and the expanded scale score [score range: 0–32; Rosenheck et al., 1991]. The latter score includes traditional combat experiences and exposures to specific events encountered during GW service (e.g., lack of communication among units, exposure to poison gas or germ warfare, placement on formal alert for chemical or biological warfare attack). In our data, the Expanded CES score was found to relate more strongly than the traditional score to increased health symptom reporting [Proctor et al., 1998]; therefore, the expanded summary score was used in the analyses.

Other covariates

Information on a number of other covariates was also determined from the questionnaire responses. These included age, gender, race, education level, repeating a grade in school, history of alcohol problem, history of head injury, being unemployed, history of occupational exposure to neurotoxicants, the number of hours of sleep on the night before testing, service in Vietnam, deployed duty status, and seeking a disability rating or upgrade. Clinical diagnoses of current major depression and current PTSD were made based on the Structured Clinical Interview for DSM III-R [Spitzer et al., 1990] and the CAPS [Blake et al., 1990], respectively. Continuous scale scores for PTSD and psychological symptomatology were determined from the Mississippi PTSD Scale modified for use with GW veterans [Keane et al., 1988] and the Brief Symptom Inventory [Derogatis, 1993], respectively. The Global Severity Index (GSI) of the Brief Symptom Inventory is a summary index and represents the most sensitive single BSI indicator of general psychological symptomatology combining information on a subject's distress level for a number of psychological symptoms and their intensity.

Analyses

The sample was weighted to account for the sampling design and response rates across sampling strata so that the weighted sample more accurately reflects the gender and symptom distribution of the larger population from which the sample was drawn. Using the SUDAAN statistical package [Shah, 1996], all analyses were adjusted for the sampling design when computing both estimates and standard errors. The tables reflect the results from these weighted analyses. For the comparison of demographic, health, and rates of psychiatric diagnoses by sample (GW-deployed vs. Germany-deployed), pairwise comparisons of means were based on a modified *t*-test and pairwise comparisons of percentages were based on a modified chi-square test (both controlling for sampling design).

TABLE I. Neuropsychological Test Battery

Functional domain tests	Description	Outcome measures
General intellectual abilities		
WAIS-R[a] information	Questions about information of the type learned in school; measure of premorbid intellectual abilities [Lezak, 1995]	Age-scaled score
Attention and executive function		
1. WAIS-R[a] digit span	Repetition of increasing number strings in forward order and in backward order; given twice	Raw score; forward and backward spans; age-scaled scores
2. WMS-R[b] digit span		
3. Continuous performance test[d]	Letters presented on computer screen; sustained attention, reaction time	Mean response time for each trial; mean reaction time over four trials; total number of false positive responses; total number of missed responses
4. Trail-making test [Reitan and Davison, 1974]	Subject must connect a series of numbered circles (A), then alternate between numbers and letters (B)	Times to complete A and B; errors in A and B
5. Paced auditory serial arithmetic test [Gronwall and Sampson, 1977]	Subject must add last two numbers in series presented orally; test of cognitive flexibility and tracking	Number correct out of 50
6. Wisconsin card sorting test [Heaton et al., 1993]	Inferential reasoning test	Number of correct sorts; number of errors
Motor/psychomotor function		
1. Finger tapping test [Halstead, 1947]	Tapping speed with index finger on tapping apparatus	Mean score of five trials with $\leq$10% variability, dominant, and non-dominant hand
2. Purdue Pegboard [Purdue Research Foundation, 1948]	Timed placement of pegs in board	Number of pegs placed by (a) dominant (b) non-dominant, and (c) both hands
Visuospatial abilities		
1. WAIS-R[a] block designs	Blocks put together in designs to match stimulus examples	Age-scaled score
Memory		
1. WMS-R[b] verbal paired associate learning	Word pairs high (4) and low (4) in associative value	Raw scores; immediate and delayed recall
2. California verbal learning test [Delis et al, 1987]	List learning task with five learning trials, interference condition, short-and long-delayed recall (cued and uncued), recognition	Raw scores for each condition
3. WMS[c] visual reproduction	Drawings of visual designs from immediate and delayed recall and to copy	Raw scores for each condition
Mood		
1. Profile of mood states [McNair et al., 1971]	Affective descriptors to which subject responds on 5-point scale; six subscales measure vigor, fatigue, anger, depression, anxiety, and confusion	T-scores for fatigue, anger, depression, anxiety, and confusion
Motivation		
1. Test of memory malingering [Tombaugh, 1996]	Simple 50-item memory test assessing tendency to purposefully perform poorly	Raw score

[a]WAIS-R: Wechsler adult intelligence scale—revised [Wechsler, 1981].
[b]WMS-R: Wechsler memory scale—revised [Wechsler, 1987].
[c]WMS: Wechsler memory scale [Wechsler, 1945].
[d]NES2: Neurobehavioral evaluation system [Letz, 1991].

Mean neuropsychological test scores, adjusted for age, education, gender, and sampling design, were compared among the GW-deployed and Germany-deployed groups using the SUDAAN statistical analysis package [Shah et al., 1996]. Also, multivariate linear regression analyses (controlling for all covariates) were performed to compare GW-deployed veterans vs. Germany-deployed veterans on all neuropsychological test outcomes (also using SUDAAN).

Additionally, a series of separate multivariate linear regression analyses was performed to explore the relationships between reported GW-specific environmental exposures (pesticides, CW agents, anti-nerve gas pills, and oil fire smoke) and neuropsychological performance within the GW-deployed groups. In order to retain the individuals who did not know if they had experienced pesticide exposure or were exposed to CW agents and left these questions unanswered, additional dummy variables were created. The results presented in the tables are for comparisons between the persons who indicated exposure vs. those who answered "no." For all multivariate linear regression analyses, saturated models (with all important covariates considered) were run. These covariates included WAIS-R Information age-scaled score, age, years of education, sex, race (Caucasian vs. other), repeated grade in school, head injury, medication use that might affect concentration, diagnosis of current PTSD (CAPS), diagnosis of current major depression (SCID), Active vs. Reserve or Guard deployment status, seeking a disability rating or upgrade, and service in Vietnam.

Due to the multiple comparisons, Bonferroni corrections (Type I error rate $< \alpha$ or $0.05/k$ number of tests; [Kleinbaum et al., 1988] were made to reduce the risk of Type I errors.

RESULTS

Subject Characteristics

Comparisons between the GW-deployed groups and the Germany-deployed group revealed no significant differences in education level, gender, repeating a grade in school, history of alcohol problem, being unemployed, history of occupational exposure to neurotoxicants, and diagnosis of PTSD (see Table II). There were significant differences in age, race, history of head injury, service in Vietnam, deployed duty status, rate of seeking a disability rating or upgrade, and level of psychological symptomatology. Compared to the GW-deployed groups, the Germany-deployed group was older, had less psychological symptomatology, and consisted (by definition) of National Guard members exclusively.

Comparison of GW-Deployed vs. Germany-Deployed Groups on Neuropsychological Test Outcomes

Multivariate regression analyses controlling for age, gender, education, and sampling design via SUDAAN revealed significant differences between the GW- and Germany-deployed groups (see Table III) in terms of mood complaints. Using a Bonferroni correction for the five POMS subscales (five measures, for overall 0.05 level, require comparison-wise *P*-values to be less than 0.01), all five subscale scores were found to differ significantly between groups. The average effect size (differences between adjusted means divided by the overall standard deviation) for the five POMS subscale scores was 0.56, with large effect sizes ranging from 0.46 to 0.62 across individual subscales.

Using a Bonferroni adjustment across individual measures within a domain, no other individual measure achieved significance. However, data from the continuous performance test (CPT) consistently suggested differences between groups, with individual *P*-values ranging from 0.04 to 0.11 on seven measures from this task. The average effect size for these measures was 0.27, with similarly moderate effect sizes ranging from 0.22 to 0.33 for individual measures. Several other individual tests of attention, executive system, and motor function were also suggestive of deficits in the GW-deployed sample (PASAT #1, WCST successful sorts, Trails A errors, Purdue Pegboard - both hands) but, after adjustment for multiple comparisons, these differences were not significant.

When comparing the neuropsychological test results between the GW-deployed and the Germany-deployed group, after controlling for all covariates, the results did not change significantly for the results presented in Table III.

Comparison of Those Who Report Specific Neurotoxicant Exposures vs. Those That Did not in GW-Deployed Groups

Results of regression analyses showed significant differences between those reporting exposure to pesticides compared to those who did not in the GW-deployed groups for all of the POMS subscales (see Table IV).

Results of regression analyses showed differences between those reporting exposure to CW agents compared to those who did not in the GW-deployed groups for the POMS subscales of tension and confusion; delayed recall on WMS Visual Reproductions; number correct on trial #2 and short delayed recall on CVLT, and the backwards raw score of the WMS-R Digit Span test (see Table V). Among the subjects who were administered the test of memory malingering (TOMM) those who reported exposure to

TABLE II. Characteristics of the Gulf-Deployed (Devens and New Orleans groups) and Non-Gulf Deployed (Germany-Deployed) Veterans Under Study (Adjusted Results Presented)

	Gulf-deployed (n = 193)	Germany-deployed (n = 47)	Significance[a]
Age in years (SE)	53.8 (0.9)	41.0 (1.3)	0.002
Education in years (SE)	13.7 (0.2)	13.7 (0.2)	0.920
WAIS-R information score (SE)	10.2 (0.3)	10.9 (0.4)	0.158
No. of hours sleep night before test (SE)	6.5 (0.1)	7.3 (0.1)	0.001
General severity index on BSI (SE)	0.60 (0.05)	0.19 (0.03)	0.001
Female(%)	13.1	12.8	0.952
Non-white Caucasian(%)	16.9	0	0.001
Repeated grade in school(%)	22.4	24.4	0.783
History of alcohol problem(%)	10.7	6.7	0.393
Diagnosis of current PTSD(%)	2.6	0	0.350
Diagnosis of current depression(%)	5.1	0	0.129
Currently taking medicine (that might affect concentration)(%)	4.0	0	0.363
Seeking disability rating or upgrade(%)	17.5	4.3	0.006
Unemployed(%)	11.9	15.6	0.560
History of head injury(%)	9.0	0	0.029
History of occupational exposure to neurotoxicants(%)	54.7	55.3	0.946
Service in Vietnam(%)	17.8	42.2	0.004
Deployed as Active duty of Gulf(%)	12.0	0	0.017

[a]SUDAAN analyses run adjusting for sampling design. Significance for categorical outcomes with 0% prevalence in the Germany-deployed group was tested through Fisher's exact test on the unadjusted data.

chemical warfare agents scored lower (adjusted mean = 45.5; SE = 1.4) compared to the unexposed group (adjusted mean = 48.3; SE = 0.53) ($P = 0.06$). This raises the question of whether malingering or motivation to perform well contributed to findings on the tests. However, when regression models were rerun for those test outcomes listed in Table V, entering TOMM scores as an additional covariate (thus controlling for the possible malingering effect in the group for which TOMM test results were available), the findings remained the same as those presented.

Separate multivariate regression analyses were also performed to look at the relationship between self-reported exposure to oil fire smoke and to pyridostigmine bromide (anti-nerve gas pills) and neuropsychological test performance. No significant results were observed for either exposure. The only exception was that those reporting oil fire smoke exposure had significantly increased scores on the POMS tension scale.

DISCUSSION

The findings from this study indicate that lower scores on neuropsychological tests are observed among the GW-deployed veteran group compared to the Germany-deployed group for several tests of attention and executive function (CPT, PASAT, WCST, and Trail Making Test) and mood states after adjustment for age, education, and gender differences. Although these data are suggestive of a deficiency in primarily affect, attention, and executive function domains among GW-deployed subjects, further study is needed to elaborate on and extend these findings. Because we examined 52 neuropsychological test outcome measures in these initial group comparisons, the multiple comparisons made raises the risk of Type I errors. With the Bonferroni correction, the only significant findings were suggestive of adverse mood effects. Similarly, when we controlled for the effects of PTSD, psychological diagnosis, estimated premorbid intellectual function, and other variables known to affect neuropsychological test performance, only adverse mood effects were observed at significant levels. Given the attenuation of significant findings when controlling for multiple comparisons, these results must be considered to be inconclusive. However, the fact that the most significant findings were seen on tests of mood should not be a basis for discounting the possibility of neurotoxicity as an underlying explanation of the findings: mood-state alterations are often closely related to dose of exposure in studies of occupational groups with well-characterized exposures (see

TABLE III. Description of the Reported Gulf-Service Environmental Exposures for the Devens and New Orleans Groups of Gulf-Deployed Veterans Under Study

	Devens (n = 140) %	New Orleans (n = 53) %
Pesticide exposure		
no exposure	45	72
exposed, but not sick	39	26
exposed, but felt sick	7	2
no answer	9	0
Anti-nerve gas pills		
no exposure	33	21
exposed, but not sick	40	38
exposed, but felt sick	26	34
no answer	1	7
Debris from Scuds		
no exposure	45	60
exposed, but not sick	47	40
exposed, but felt sick	4	0
no answer	4	0
Oil fire smoke		
no exposure	14	30
exposed, but not sick	60	38
exposed, but felt sick	26	32
no answer	0	0
CBW agents		
no exposure	57	68
exposure	19	13
no answer	24	19

below). Furthermore, we controlled for psychiatric diagnoses and PTSD in the analyses. Our findings are similar to those described by Anger et al. [1999] in that they do not suggest a widespread pattern of neurobehavioral deficits in GW-deployed veterans, but rather there may be subgroups of veterans with subtle impairments.

Two GW service-related exposures that were hypothesized *a priori* to be particularly likely to be associated with neuropsychological outcome are exposure to pesticides and chemical warfare agents. A number of pesticides are known to be neurotoxic. For example, organophosphates and carbamates have been known to be neurotoxicants for some time [White et al., 1990], and there are a number of papers linking pesticide exposure to CNS dysfunction [Rosenstock et al., 1991; Savage et al., 1988; Steenland et al., 1994], typically in a few behavioral domains, including mood. Likewise, sarin and mustard gas are known to act directly upon the CNS, with residual effects on motor function [Yokoyama et al., 1998], neurophysiological measures [Murata et al., 1997], short-term memory and mood [Jamal, 1995]. In this study, subjects who on questionnaire reported exposure to pesticides complained of more affective symptoms than subjects without such exposure on validated and reliable measures that assess mood state (i.e., POMS) given at a separate point in time. Subjects reporting chemical warfare exposures performed more poorly on tests assessing short-term memory (CVLT, WMS Visual Reproductions), attention (WAIS-R Digit Span backwards), and mood (POMS), domains that are known to be particularly susceptible to the effects of neurotoxicants [White, 1992; White and Proctor, 1997]. While the argument could be proffered that subjects reporting these specific exposures "believed" that they might have CNS dysfunction as a result of their exposures and therefore performed more poorly on neuropsychological test measures, it does not seem likely that subjects would know which of the exposures that they experienced in the Gulf were particularly likely to affect the CNS vs. other body systems, nor does it seem likely that these individuals would know CNS dysfunction would be confirmable using neuropsychological tests. Furthermore, subjects with self-reported chemical warfare agent exposures showed more deficits relative to the unexposed subjects than those with exposures to insecticides and pesticides, perhaps reflecting the relatively greater neurotoxicity of the former substances.

While the neuropsychological effects described by prior investigators have been explainable on the basis of psychiatric status [Goldstein et al., 1996; Sillanpaa et al., 1997] or PTSD [Vasterling et al., 1997], controlling for these covariates does not completely explain the current findings vis-à-vis exposure effects. It might be argued that the POMS results confirm the existence of dysphoria in the exposed groups and could be used as a basis for explaining the neuropsychological test findings. However, when the analyses already described were re-run using POMS depression *t*-score as a covariate, the results for the cognitive tests were largely the same. Furthermore, it is very difficult to tease out cause–effect relationships in a cross-sectional study when one is dealing with exposures to neurotoxicants, CNS dysfunction caused by such exposures, and affective disorders and symptomatology. Several studies have demonstrated dose–effect relationships between exposure to neurotoxicants and degree of negative affect on the POMS scales. Baker and colleagues [Baker et al., 1984, 1985], for example, showed that subjects with higher blood lead levels had more intensive mood complaints on the POMS than those with lower blood lead levels (subjects did not know their lead levels when they completed the POMS) and that as lead levels dropped across testing dates, POMS scores declined also. Subjects with naphtha exposure blind to their levels of exposure also showed higher POMS scores with higher acute naphtha exposure [White et al., 1994]. The results of these and other studies, therefore, suggest that

TABLE IV. Gulf (Devens and New Orleans Groups) vs. Non-Gulf Deployed (Germany-Deployed) Group Comparisons (Adjusted Means [SE])

	Gulf-deployed (n = 193)	Germany deployed (n = 47)	Significance†
General intellectual abilities			
WAIS-R information, age-scaled score	10.3 (0.22)	10.5 (0.37)	0.731
Attention and executive system functions			
WAIS-R digit span raw score	15.8 (0.39)	16.1 (0.62)	0.705
WAIS-R forward digit span	7.0 (0.11)	7.0 (0.19)	0.795
WAIS-R backward digit span	5.0 (0.13)	5.3 (0.22)	0.311
WMS-R, digit span raw forward	9.0 (0.18)	8.7 (0.34)	0.455
WMS-R, digit span, forward	7.0 (0.09)	6.7 (0.19)	0.135
WMS-R, digit span raw, backward	7.4 (0.23)	7.5 (0.35)	0.859
WMS-R, digit span, backward	5.3 (0.13)	5.4 (0.21)	0.486
CPT, trial 2 mean reaction time	356.0 (6.7)	339.9 (7.3)	0.110
CPT, trial 3 mean reaction time	366.1 (6.9)	347.3 (7.5)	0.077
CPT, trial 4 mean reaction time	382.0 (7.4)	360.0 (7.4)	0.041
CPT, trial 5 mean reaction time	379.8 (6.9)	361.0 (8.0)	0.079
CPT, total–mean reaction time	371.0 (6.6)	352.1 (7.0)	0.058
CPT, total # false positives	1.35 (0.30)	0.80 (0.18)	0.098
CPT, total # non-responses	0.33 (0.12)	0.11 (0.07)	0.067
PASAT #1, number correct	38.0 (0.86)	41.4 (1.3)	0.037
PASAT #2, number correct	32.6 (0.93)	35.2 (1.5)	0.136
PASAT #3, number correct	28.5 (0.89)	27.5 (1.5)	0.574
PASAT #4, number correct	22.0 (0.82)	23.3 (1.2)	0.373
WCST, # of successful sorts	3.51 (0.12)	3.79 (0.20)	0.025
WCST, # of errors	16.5 (0.78)	14.9 (1.2)	0.298
TRAILS A, time in seconds	28.4 (0.65)	26.5 (1.0)	0.139
TRAILS A, errors	0.31 (0.06)	0.08 (0.06)	0.015
TRAILS B, time in sec.	69.0 (2.7)	64.3 (3.9)	0.359
TRAILS B, errors	0.41 (0.13)	0.21 (0.16)	0.439
Motor/psychomotor abilities			
Finger Tapping, dom. hand – 5 trial mean	54.3 (0.6)	54.8 (1.1)	0.687
Finger Tap, non-dom. hand – 5 trial mean	49.1 (0.5)	48.7 (1.1)	0.725
Purdue Pegboard, dominant hand	14.6 (0.16)	14.7 (0.27)	0.762
Purdue Pegboard, non-dominant hand	13.5 (0.16)	14.0 (0.26)	0.143
Purdue Pegboard, both hands	11.0 (0.15)	11.8 (0.24)	0.013
Visuospatial constructional abilities			
WAIS-R Block Design, age-scaled score	11.0 (0.24)	11.5 (0.36)	0.303
Memory			
Verbal PAL, easy items only, immediate	10.4 (0.14)	11.0 (0.20)	0.032
Verbal PAL, easy items only, delay	4.0 (0.01)	4.0 (0.03)	0.652
Verbal PAL, difficult items only, immediate	5.7 (0.22)	5.9 (0.39)	0.632
Verbal PAL, difficult items only, delay	3.2 (0.09)	3.4 (0.13)	0.251
CVLT, trial 1, number correct	7.4 (0.18)	7.3 (0.27)	0.935
CVLT, trial 2, number correct	10.1 (0.19)	10.3 (0.27)	0.648
CVLT, trial 3, number correct	11.8 (0.18)	11.4 (0.31)	0.294
CVLT, trial 4, number correct	12.2 (0.20)	12.3 (0.33)	0.866
CVLT, trial 5, number correct	12.9 (0.18)	13.0 (0.32)	0.948
CVLT Tuesday list-# correct	6.5 (0.20)	7.2 (0.26)	0.032
CVLT, short delay recall #correct	11.7 (0.23)	11.5 (0.31)	0.789
CVLT, long delay recall, #correct	11.7 (0.29)	11.8 (0.39)	0.918

TABLE IV. (*Continued*)

	Gulf-deployed (n = 193)	Germany-deployed (n = 47)	Significance[a]
CVLT, # correct on recognition	14.5 (0.22)	15.1 (0.22)	0.141
WMS visual reproductions, immediate	10.4 (0.23)	10.2 (0.37)	0.613
WMS visual reproductions, delayed recall	9.6 (0.25)	9.2 (0.43)	0.454
WMS visual reproductions, copy	12.5 (0.13)	12.7 (0.16)	0.221
Mood			
POMS tension *t*-score	39.2 (0.62)	35.8 (0.90)	0.003
POMS depression *t*-score	40.2 (0.54)	36.4 (0.53)	0.001
POMS anger *t*-score	45.0 (0.61)	40.6 (0.85)	0.001
POMS fatigue *t*-score	47.4 (0.62)	42.1 (0.84)	0.001
POMS confusion *t*-score	41.5 (0.55)	37.2 (0.67)	0.001
Motivation			
TOMM: trial1[b]	48.0 (0.44)	48.2 (0.65)	0.723

[a]SUDAAN analyses: adjusted for age, education, gender, and sampling design. Comparisonwise *P*-values not adjusted for multiple comparisons are presented.
[b]TOMM was performed for a subsample of 74 Gulf-deployed and 47 Germany-deployed subjects.

negative affective symptoms are a result of neurotoxicant exposure and constitute one feature of the behavioral and cognitive changes resulting from CNS damage linked to exposure to neurotoxicants. Affective changes related to exposures often appear as temporary changes in mood states, not as formal psychiatric syndromes of the type that are diagnosed with psychiatric interview scales such as the SCID or CAPS that were used in the present study to diagnose depression and PTSD. Because of findings of this nature, the POMS is included on several recommended test batteries in assessing neurotoxicity, such as the World Health Organization Battery [Cassitto et al., 1990] and the Agency for Toxic Substances and Disease Registry battery [Hutchinson et al., 1992].

Given the issue of possible disability benefits arising from injuries sustained during GW service, one could wonder whether GW veterans who thought that they were exposed to chemical or biological warfare agents might perform more poorly on neuropsychological tasks in order to document some form of functional damage. Using this argument to explain the current findings pre-supposes that the veterans with specific exposures would know which tests to "fail" and would, in fact, fail many tests. The findings for subjects with self-reported chemical warfare exposure are limited to a few rather difficult tests on memory and complex attention (see Table VI). Moreover, assessment of motivation and malingering in the subset that were administered the TOMM did not identify significant faking or malinger-

TABLE V. Reported Pesticide Exposure vs. None (For Devens and New Orleans Groups of Gulf-Deployed Veterans, n = 171)[a]

Domain	Test	Adj. multiple R^2	Adj. mean (SE) Pesticide-exposed (n = 65)	Adj. mean (SE) Unexposed (n = 88)
Mood	POMS tension	0.252	41.3 (1.0)*	37.6 (0.71)
	POMS depression	0.421	41.4 (0.87)*	39.2 (0.53)
	POMS anger	0.234	46.9 (1.2)*	43.4 (0.77)
	POMS fatigue	0.171	49.4 (1.3)*	46.2 (0.75)
	POMS confusion	0.348	43.9 (0.97)*	40.0 (0.63)

[a]Run in SUDAAN- saturated model of covariates included: WAIS-R information age-scaled score, age, years of education, sex, race (Caucasian vs. other), repeated grade in school, head injury, medication use that might affect concentration, diagnosis of current PTSD (CAPS), diagnosis of current major depression (SCID), Active vs. Reserve or Guard deployment status, seeking a disability rating or upgrade, service in Vietnam.
*Comparing exposed to those reporting no exposure: $P \leq 0.05$.

TABLE VI. Reported Chemical Warfare (CW) Exposure vs. None (For Devens and New Orleans Groups of Gulf-Deployed Veterans, n=171)[a]

Domain	Test	Adj. multiple R^2	Adj. mean (SE) CBW exposure (n = 27)	Adj. mean (SE) Unexposed (n = 102)
Mood	POMS tension	0.202	41.1 (1.4)*	37.6 (0.72)
	POMS confusion	0.315	43.4 (1.2)*	39.8 (0.65)
Memory	WMS Visual Reprod.			
	Delayed recall	0.363	8.3 (0.46)*	9.8 (0.31)
	CVLT trial 2, # correct	0.315	9.4 (0.37)*	10.5 (0.27)
	CVLT short delayed recall	0.399	10.4 (0.53)*	11.9 (0.28)
Attention and Executive function	WMS-R digit span Backward raw score	0.381	6.6 (0.35)*	7.6 (0.26)

[a]Run in SUDAAN- saturated model of covariates included: WAIS-R information age-scaled score, age, years of education, sex, race (Caucasian vs. other), repeated grade in school, head injury, medication use that might affect concentration, diagnosis of current PTSD (CAPS), diagnosis of current major depression (SCID), Active vs. Reserve or Guard deployment status, seeking a disability rating or upgrade, service in Vietnam.

*Comparing exposed to those reporting no exposure: $P \leq 0.05$.

ing. In addition, disability application status was controlled for in the analyses.

In summary, this study suggests that there are subtle impairments in cognitive function as measured by objective tests and in mood state that can be linked to Gulf War service and to self-reported exposures in the Gulf War theater. These impairments, in turn, raise the possibility of CNS damage that is linked to specific self-reported exposures (i.e., CW agents). Further exploration of relationships between exposure to toxicants and CNS function are underway. In these studies, we are taking several approaches, including assessing the relationship between self-reported neuropsychological symptoms and performance on neuropsychological tests and further examining the relationship between lower scores on the memory and malingering test and diagnostic outcomes. We are also examining exposure–response relationships in other GW-deployed populations (i.e., DVA treatment-seekers, a group of Danish military personnel deployed to the Gulf for clean-up operations). In addition, other means of modeling exposure to toxicants (i.e., geographical information systems) are being used to explore possible relationships between exposure, health symptomatology, and cognitive test performances. Finally, functional neuroimaging techniques are being used to corroborate the neuropsychological test findings.

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Chemical Sensitivity and Chronic Fatigue in Gulf War Veterans: A Brief Report

Susan P. Proctor DSc
Kristin J. Heaton, MS
Roberta F. White, PhD
Jessica Wolfe PhD, MPH

The foci of this brief report are to (1) describe the prevalence of chemical sensitivity (CS) and chronic fatigue (CF) symptomatology and of presumptive multiple CS and CF syndrome diagnoses, and (2) explore the potential overlap between one purported case definition (ie, chronic multi-symptom illness) and these unexplained symptom syndromes in a well-characterized group of Gulf War veterans. The number of subjects with CS and CF symptomatology and presumptive multiple CS and CF syndrome diagnoses was higher in the Gulf War–deployed group compared with a group deployed to Germany during the Gulf War. However, the percent differences were not significant when comparing the presumptive diagnoses of multiple CS and CF syndrome. The characteristic differences between the groups and the overlap with chronic multi-symptom illness are also discussed. (J Occup Environ Med. *2001;43:259–264*)

Since returning to the United States from service in the Persian Gulf during Operation Desert Storm, Gulf War (GW) veterans have reported elevated numbers of various physical and psychological health symptoms compared with non–GW-deployed groups.[1–6] In an attempt to better understand this complex symptomatology, studies have explored the proposition that the symptoms experienced by GW veterans can be defined by a specific case definition (such as chronic multi-symptom illness [CMI][7]) or by a group of several case definitions (such as the symptom clusters proposed by Haley et al).[3] Rather than defining GW veterans' illnesses, other studies have followed a different research approach and examined the prevalence of the unexplained symptom syndromes of chronic fatigue syndrome (CFS) and multiple chemical sensitivities (MCS) and associated risk factors in GW veterans.[8–10]

The foci of this brief report are to (1) describe the prevalence of chemical sensitivity (CS) and chronic fatigue (CF) symptomatology and of presumptive MCS and CFS diagnoses, and (2) explore the potential overlap between one purported case definition (ie, CMI) and these unexplained symptom syndromes in a well-characterized group of GW veterans. The percentage of GW-deployed veterans with these outcomes is compared with that observed in a sample of military personnel who were deployed to Germany at the time of the GW. Based on the general consensus in the literature that GW veterans are

From the Boston Environmental Hazards Center (Dr Proctor, Ms Heaton, Dr White, Dr Wolfe), the National Center for PTSD (Dr Proctor, Dr Wolfe), and Psychology Service (Dr White, Dr Wolfe), VA Boston Healthcare System; the Boston University School of Public Health (Environmental Health) (Dr Proctor, Dr White); the Boston University School of Medicine (Neurology) (Dr Proctor, Dr White); the Boston University School of Medicine (Psychiatry) (Dr White, Dr Wolfe); and the University of Southern Denmark, Department of Environmental Medicine, Odense (Dr White).

Address correspondence to: Susan P. Proctor, DSc, Boston Environmental Hazards Center (116B-4), 150 South Huntington Avenue, Boston, MA 02130-4893; e-mail: sproctor@bu.edu.

reporting high rates of various health symptoms, it is hypothesized that higher rates of CS and CF symptomatology, of presumptive MCS and CFS, and of CMI will be observed in the GW-deployed group compared with the Germany-deployed group.

Methods

Subjects

Subjects in this study were 180 veterans from a larger cohort of military personnel deployed to the Gulf (Devens Cohort) who had previously been studied at two time points since their return from the GW: the first study phase took place in spring 1991 and the second was 18 to 24 months later.[11–13] The current study phase (time 3) was conducted between 1994 and 1996, when a stratified, random sample of the original cohort was asked to participate. The sampling technique was designed to ensure equal representation of both lower and higher symptom reporters (based on a median split of the time 2 symptom checklist responses) and to oversample for women. A more complete description of the Devens Cohort and the sampling scheme used in this study phase can be found in previous publications.[5,14] These participating veterans represented 29 units serving in the GW and consisted primarily of transportation crews, military police and security personnel, medical personnel, road construction and combat engineering personnel, and reclamation crews (aircraft and parts).

A group of 46 veterans deployed to Germany as part of Operation Desert Shield/Storm served as the comparison group for the Devens Cohort sample because both shared similar deployment-related stressors (eg, leaving one's family and job, deployment overseas) and were deployed at about the same time and under similar conditions (Operation Desert Shield/Storm). This group consisted of members of a Maine National Guard air ambulance unit deployed to Germany during Operation Desert Storm (December 1990 to August 1991). Unit members included helicopter pilots, flight crews, medics, mechanics, communication specialists, and administrative support personnel deployed to assist in the transport and handling of wounded US servicemen and women evacuated from the Gulf. Because of the low number of US causalities in the Gulf, the unit also assisted with civilian evacuations in Germany and conducted transport missions.

Study Protocol

The subjects completed medical and occupational history questionnaires and several measures that assessed psychological symptomatology (eg, Brief Symptom Interview,[15] Mississippi Post-Traumatic Stress Disorder [PTSD] Scale).[16] An environmental interview, a neuropsychological test battery, and psychological diagnostic interviews (Structured Clinical Interview for *Diagnostic and Statistical Manual,* 3rd Edition, Revised[17] and Clinician Administered PTSD Scale[18]) were also conducted. The protocol was approved by the Institutional Review Board, and written informed consent was obtained from each participant. This report focuses primarily on information obtained from the questionnaire and the environmental interview regarding CS, CF, and general health symptoms. For a review of the overall environmental interview structure, see Proctor.[19] All of the environmental interviews were conducted by a trained environmental health professional (S.P.P.).

Measures

Demographic and covariate information. Demographic information was obtained from questionnaire responses regarding gender, age, and highest level of education achieved. The Global Severity Index of the Brief Symptom Inventory[15] is a summary index that represents the most sensitive single Inventory indicator of a subject's psychological distress level by combining information on a number of psychological symptoms and their intensity. We used a standard scoring protocol that permits a determination of positive psychiatric case status based on relevant normative samples. The structured psychological diagnostic interviews provided clinical diagnostic information for current and lifetime Axis I disorders. The most prevalent diagnoses among the GW-deployed group were major depression and post-traumatic stress disorder.[14]

Presumptive MCS and CS symptomatology. Subjects who noted during the environmental interview that they had health symptoms that were triggered by chemical odors were questioned to determine whether they met the research criteria for MCS syndrome, as adapted from Cullen's research criteria.[20] These a priori criteria required that the participant report (1) more than one symptom that began after service in the Persian Gulf or in Germany, (2) symptoms that involve more than one organ system, (3) symptoms triggered by low-level exposures to chemicals, and (4) symptoms that cannot be explained by any diagnosis or medical information obtained from the questionnaires. Subjects were not excluded for having a concurrent psychiatric diagnosis (based on clinical psychiatric diagnostic interviews) or for having self-reported asthma; however, this information was noted if relevant. An endorsement of CS symptomatology was given to subjects who reported symptoms(s) on interview that were triggered by low-level exposures to common chemicals but failed to meet the remaining criteria. In addition, subjects were considered to have CS symptomatology if they met one of three criteria, as assessed from their responses to the section of the medical questionnaire addressing chemical sensitivities. The first criterion, taken from Simon et al,[21] required a positive response to at least one of four questions addressing lifestyle changes (eg, "Do you now need to wear particular clothes because of

chemical sensitivity?"). The second criterion required that subjects respond positively to at least one of four questions ascertaining food and/or alcohol aversions that began or worsened after their service in the GW (eg, "Does drinking a small amount of alcohol make you feel ill?"). The final criterion required a positive response to feeling ill after exposure to at least one of 12 common odors after their service in the GW. These 12 exposures included new carpeting, insecticides, tobacco smoke, paint thinner, natural gas, perfume/cologne, detergents, hair spray, drying paint, diesel or gas engine exhaust, gasoline, and chlorinated water.

Presumptive CFS and CF symptomatology. Subjects who reported fatigue as a current health symptom on the environmental interview were queried to determine whether they met the criteria for CFS as outlined by Holmes et al[22] and Fukuda et al.[23] For this brief report, we include the rates using the 1994 criteria (the currently recognized and accepted criteria). For a subject to be categorized as having CFS, he or she had to report fatigue that (1) began after returning from the GW, (2) lasted for more than 6 months, (3) did not improve with bed rest, (4) resulted in substantial reduction in average daily activities, and (5) was accompanied by at least four of eight symptoms (self-reported short-term memory loss; sore throat; tender cervical or axillary lymph nodes; muscle pain; multi-joint pain without joint swelling/redness; headaches of a new type, pattern, or severity; unrefreshing sleep; postexertional malaise lasting for more than 24 hours). In addition, the subject must not have indicated any concurrent medical or psychiatric conditions on the questionnaire or during the clinical psychiatric interviews that would rule out a diagnosis of CFS, based on the exclusion or rule-out indications specifically described by Fukuda et al[23] (eg, substance abuse, bipolar affective disorder). Subjects who indicated in the environmental interview that they had current feelings of fatigue but did not fully meet the 1994 CFS criteria were categorized as having CF symptomatology.

CMI. There was considerable duplication between the health symptoms queried in our study questionnaire and those symptoms and conditions contained in the Centers for Disease Control and Prevention case definition for CMI.[7] Thus, we were able to determine which subjects in our study sample met the case definition for CMI. To be identified as having CMI, the subjects were required to report at least one symptom each from two of the three symptom clusters set forth by the Centers for Disease Control and Prevention: fatigue, mood and cognition, and musculoskeletal. In our questionnaire, these clusters were defined by symptom endorsements of (1) fatigue or easily tired; (2) frequent periods of feeling depressed, forgetfulness, difficulty concentrating, crying easily, excessive anger or irritability, frequent periods of anxiety and nervousness, inability to fall asleep, restless or unsatisfying sleep, or awake earlier than desired; and (3) neck aches or stiffness or joint pains. In addition, symptoms had to have begun either during or since service in the GW but not before, and each symptom endorsed had to be at least 6 months in duration. We followed the distinction between mild-to-moderate and severe cases set forth by the Centers for Disease Control and Prevention, whereby symptoms reported as occurring rarely or sometimes were designated as mild-to-moderate and symptoms reported as occurring often or very often were designated as severe.

Analyses

The descriptive characteristics and prevalence rates of CS and CF symptomatology, and of presumptive MCS, CFS, and CMI, were determined and compared between the GW and Germany-deployed groups. All analyses (unless otherwise noted) were conducted using the SUDAAN statistical analyses package[24] that weighted the sample groups to account for the stratified sampling design. Logistic regression analyses were performed by controlling for age and psychological case status (using the Global Severity Index cut-score) differences between the two groups for those outcomes in which there was a non-zero prevalence (for CS and CF symptomatology and for CMI). Analyses to examine the overlap between the three groups of outcomes (ie, CMI, CS-related outcomes, and CF-related outcomes) were performed using the Statistical Package for the Social Sciences (version 9.0).

Results

Group characteristics (age, educational level, gender, and psychiatric diagnostic status) are presented for the GW- and Germany-deployed samples in Table 1. The GW-deployed sample was significantly younger than the Germany-deployed sample. In addition, a higher percentage of the GW-deployed group met psychiatric case criteria. There were no significant differences between these groups with regard to level of education or gender.

The rates of CS and CF symptomatology and overall CMI (and "severe" CMI) were significantly higher in the GW-deployed group than in the Germany-deployed group. However, there were no significant differences between the groups with respect to presumptive MCS or CFS or in the percentage of subjects with the "mild-to-moderate" CMI case designation. Three of the four subjects from the GW-deployed cohort who met criteria for presumptive MCS also met the 1994 criteria for CFS without adjusting for exclusionary, rule-out diagnoses; one subject (of the four) met the criteria for both presumptive MCS and CFS.

Results from logistic regression analyses, adjusted for sampling design and controlled for age and psy-

TABLE 1
Group Characteristics and Comparison of Outcome Rates*

	GW-Deployed (n = 180)	Germany-Deployed (n = 46)	Significance Level†
Mean age in years ± SE	36.5 ± 0.92	40.8 ± 1.35	0.008
Mean education level ± SE	13.5 ± 0.18	13.8 ± 0.22	NS
Female (%)	10.6	13.0	NS
Psychiatric case, based on BSI-GSI cut-score (%)	38.6	6.5	<0.001
Clinical psychiatric diagnosis on SCID/CAPS (n = 143) (%)	16.8	0	[0.001]
Chemical sensitivity (%)	14.3	2.2	0.001
Presumptive MCS (%)	2.9‡	0	[NS]
Chronic fatigue (%)	29.4	8.7	<0.001
Presumptive CFS (%)			
Meets 1994 criteria before rule-out	7.5	0	[0.02]
Meets 1994 criteria after rule-out	2.0§	0	[NS]
CMI case (%)	65.3	32.6	<0.001
Mild-to-moderate	33.4	28.3	NS
Severe	31.9	4.4	<0.001

* GW, Gulf War; SE, standard error; NS, not significant ($P > 0.05$); BSI, Brief Symptom Inventory; GSI; Global Severity Index; SCID, Structured Clinical Interview for Diagnostic and Statistical Manual, 3rd Revision; CAPS, Clinical Assessment for Post-Traumatic Stress Disorder; MCS, multiple chemical sensitivity syndrome; CFS, chronic fatigue syndrome; CMI, chronic multi-symptom illness. Comparisons between groups were performed by using SUDAAN. The rates and means (SE) presented are adjusted for sampling design.

† The significance levels given for the comparison between groups where the categorical outcomes are 0% prevalence in the Germany-deployed group are from the Fisher's exact test (2-sided) on the unadjusted data and are presented in brackets. Otherwise, the significance levels reported are from the chi-squared statistic produced by SUDAAN analyses.

‡ Two of the four MCS cases had an asthma diagnosis, and an overlapping two of the four had either current or lifetime psychiatric diagnosis on SCID or CAPS.

§ The majority of those ruled-out or excluded were for current or recent alcohol or substance abuse.

chiatric case status, found that the GW-deployed group was at higher risk for CS and CF symptomatology and for CMI than the Germany-deployed group (odds ratio = 8.4, 4.5, and 2.4, respectively). However, only for CMI was the odds ratio significantly greater than 1 (ie, 95% confidence interval = 1.1, 5.3).

Some overlap occurred among those subjects who met the case definition for CMI, those with either CS symptomatology or presumptive MCS, and those with either CF symptomatology or presumptive CFS. Within the GW-deployed group, 12.2% (n = 22) met the criteria for all three outcome categories concurrently, and 27.8% (n = 50) did not meet the criteria for any of the three outcomes. In the Germany-deployed group, none of the subjects met the criteria for all three outcome categories simultaneously, and 58.7% (n = 27) did not meet the criteria for any of the three outcomes.

Discussion

The number of subjects with CS and CF symptomatology and presumptive MCS and CFS diagnoses was higher in the GW-deployed group compared with the Germany-deployed group. However, the percent differences were not significant when comparing the presumptive diagnoses of MCS and CFS. This suggests that although there were significantly more reports of CS and CF symptomatology in the GW-deployed group compared with the Germany-deployed group, there were no differences in the number of subjects who met the presumptive diagnostic criteria for these unexplained symptom syndromes.

The frequency of presumptive MCS in this GW-deployed population (2.9%) was comparable with the rate seen in a recent community study of MCS (6%)[25] and was in the lower end of the range observed in other GW veteran cohort studies (ie, 2% to 6%).[2,8,9] The percentage of subjects with presumptive CFS in the GW-deployed population (2%) was somewhat higher than that found in a recent US population study (ie, 0.42%[26]) but was comparable with the frequency found in a study of GW-deployed veterans from the United States (1.5%)[1] and the United Kingdom (3.3%).[27] However, as has been observed in most studies to date involving these unexplained symptom syndromes, the methods of outcome assessment and the study populations were not exactly the same, thus restricting study comparison and interpretation of collective results. For example, our study's assessment procedure followed the recognized diagnostic criteria for CFS; however, in the interest of increasing the subject's compliance and reducing the overall time burden for the subject, we did not include the recommended laboratory tests or clinical evaluation by a physician as was done in the study by Jason and colleagues.[26] For this reason, we refer to

the outcome as presumptive CFS. Nevertheless, our study's outcome assessment methods were similar to the phase 1 criteria of the study by Jason et al,[26] in which they report that a comparable 2.2% of subjects screened positive for CFS-like illness.

Some overlap occurred between the subjects who met the criteria for CMI and concurrently for the unexplained symptom syndrome entities involving chemical sensitivities and CF within the GW-deployed group. Also, those with either CF or CS symptomatology or presumptive diagnoses for CFS or MCS were more likely to meet the CMI case definition (77 of the 82 subjects who met the criteria for CS or CF symptomatology or presumptive CFS or MCS also met the CMI criteria). These findings suggest that the probability that a person has CMI given that they have either MCS or CFS is very high (sensitivity = 94%), but the probability that a person does not have CMI given that they have neither MCS or CFS is low (specificity = 51%). Therefore, if one assumes that CMI defines those GW veterans who are ill, then the GW veterans with MCS or CFS symptomatology would likely be classified as ill. However, a considerable number of ill GW veterans will not have CS or CF-related symptomatology or clinical presentations. It is interesting to note that the number of persons with CMI at the mild-to-moderate levels is similar in both the GW- and Germany-deployed groups; thus, the specificity of CMI as an indicator of GW-related illnesses is questionable.

Although this study has several limitations, such as its relatively small sample size and its lack of full-scale medical or laboratory evaluations for all of the proposed exclusionary conditions for MCS and CFS, the study does have a number of unique strengths that further extend the knowledge and understanding of these syndromes within the GW-veteran population. In contrast to the study by Kipen et al[10] of self-selected VA Registry participants, we examined a cohort of New England-area GW veterans and a comparison group of military personnel who were deployed to Germany for their GW deployment tour of duty. Thus, we believe that our findings are more generalizable to the overall population of GW veterans than were those on the VA Registry, at least more comparable with those military personnel deployed to the GW from the New England area. Also, as part of the study protocol, we used a tiered assessment approach that included a priori diagnostic criteria for MCS and CFS and methods to assess symptomatology. As a result, we were able to examine these outcomes while presuming two levels of severity, one being symptomatology criteria and lifestyle changes, the other being comparable with a priori case definitions.

Disagreement exists about whether a single case definition for GW veterans' health concerns can be proposed and whether it is appropriate.[28] A number of investigators and government panel reports[29,30] conclude that GW veterans' health issues involve a number of different outcome presentations and have multiple etiologies. Continued focused epidemiological research that explores the overlapping distribution and various risk factors associated with current working case definitions (for a current listing see Appendix III in the recent General Accounting Office Report[28]), along with new categorizations, in GW and comparison populations is warranted to test the usefulness of these syndrome categorizations in explaining GW veterans' health concerns.

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Health-Related Quality of Life in Persian Gulf War Veterans

Guarantor: Susan P. Proctor, DSc
Contributors: Susan P. Proctor, DSc*†‡‖; Rebecca Harley, MA§‖; Jessica Wolfe, PhD MPH*§‖††; Tim Heeren, PhD*¶; Roberta F. White, PhD ABPP*†‡§**

Objective: The objective of this investigation is to describe the health-related quality of life of Persian Gulf War (GW) veterans and to examine the effects of current chronic medical conditions and psychiatric status on physical functioning. Methods: To measure health-related quality of life, the Medical Outcomes Short Form Survey (SF36) was administered approximately 4 years after the GW to a stratified, random sample of New England-area GW-deployed veterans and a group of military personnel deployed to Germany during the GW. The SF36 scores for the GW-deployed study population (N = 141) were compared with those for the Germany-deployed group (N = 46) and with published U.S. population norms. Multiple linear regression analyses were performed to identify risk factors associated with lower physical health functioning in the GW-deployed study group. Results: Functional health status was significantly lower in the GW-deployed group compared with the Germany-deployed group for each of the SF36 subscales and the two summary scores (Physical Component Summary [PCS] and Mental Component Summary). Compared with the general U.S. population, the GW-deployed group median was between the 25th and 50th percentile for the Physical Functioning subscale and the PCS score. Within the GW-deployed group, lower education, psychological symptomatology, and a higher number of chronic self-reported medical conditions were significant predictors of the PCS score. Conclusion: GW-deployed veterans report lower functional health status compared with a group of Germany-deployed veterans and published general U.S. population norms. Within the group of GW-deployed veterans, several current medical and psychological conditions predictive of lower physical functioning levels were identified.

Introduction

Most U.S. troops returned home from the Persian Gulf War (GW) in the spring of 1991, and many began reporting adverse health symptoms and chronic medical problems soon after.[1,2] Recently, epidemiological studies have noted increased health symptomatology in GW-deployed troops compared with other GW-era veterans.[3-9] An important issue is how increased symptomatology might be reflected in the health-related quality of life of GW veterans. This issue is of considerable importance for the veterans, the Department of Defense, and the Department of Veterans Affairs (DVA) in their attempt to understand and improve veterans' functional health status. Documenting and understanding the characteristics of veterans' functional health status and well-being that affect daily life (referred to as health-related quality of life) are important aspects of recently initiated DVA treatment trials involving GW veterans[10,11] and of ongoing epidemiological and clinical studies examining the potential risk factors surrounding GW veterans' health problems.

The Medical Outcomes Study Short Form Survey (SF36) is a well-validated tool for the measurement of functional health status.[12-14] Extensive norms from a general U.S. population group and for persons with various medical conditions have been published[15,16] that permit examination of the relationship between health and medical outcomes and functional health status. Few published studies have described the assessment of functional health status in U.S. military populations. However, this information may be forthcoming, because recent Department of Defense health surveillance initiatives include plans to survey all new military recruits to obtain baseline medical and functional health information[17] (including questions from the SF36; Craig Hyams, personal communication).

One objective of this article is to describe the health-related quality of life, as measured by the SF36, in a group of GW veterans deployed from the New England area who are not necessarily seeking DVA care or treatment. Several studies suggest that those veterans using DVA ambulatory care services have poorer functional health status than the general U.S. population (based on published norms).[18,19] However, little is published about the functional health status of veterans in general or those not seeking treatment at DVA health services, and more specifically, of GW veterans. One might hypothesize that those persons more physically fit would be more likely to enlist, serve, and remain in military service, and thus, that active duty military personnel and/or recently deployed military personnel would have better physical functional health status than the general U.S. population as a result of self-selection characteristics and preparation and training regimens. Several recently published epidemiological studies,[3,5-7] registry studies,[20,21] and other ongoing population-based studies, such as the DVA's National Health Survey,[22] have examined GW veterans' health issues using survey protocols that included the SF36. However, to our knowledge, only two of the investigations[3,7] have published comparisons between their respective GW veteran samples and the nondeployed (or GW-era) comparison groups; both indicated poorer functioning in the GW-deployed groups.

Building on work by Kazis and colleagues,[18,23] who found that particular medical conditions (e.g., low back pain and chronic lung problems) appear to be important risk factors for diminished functional health status in DVA treatment-seeking veterans, another objective of this investigation is to examine the effect of current medical conditions on physical functioning in a group of GW-deployed veterans.

*Boston Environmental Hazards Center, §Psychology Service, and ‖National Center for PTSD, VA Boston Healthcare System, Boston, MA.
†Department of Environmental Health, and ¶Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston, MA.
‡Department of Neurology, and ††Department of Psychiatry, Boston University School of Medicine, Boston, MA.
**Department of Environmental Medicine, Odense University, Odense, Denmark.
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We hypothesized that GW-deployed veterans would have lower physical functional health status compared with a group of military personnel deployed to Germany during the GW. Both groups were administered the SF36 when they were studied 4 years after the GW. Additionally, we expected that GW-deployed veterans would have better functional status than that observed in the general U.S. population. We also anticipated that, within the GW-deployed veterans, current medical and psychiatric conditions would be significant risk factors for decreased physical functioning.

The aims of this article are as follows: (i) to report characteristics of this GW veteran sample in terms of disability status, disease prevalence, and health-related quality of life; (ii) to compare SF36 subscale scores in the GW-deployed group with those measured in a group deployed to Germany during the GW and with published U.S. population norms; (iii) to report differences in functional health between GW veteran subgroups with and without medical and/or psychological disorders; and (iv) to identify risk factors predictive of poorer physical functioning measures.

Increasingly, military and veterans' health studies are using the SF36 as a measure of functional health status, either as a surveillance measure to assess predeployment and postdeployment health changes or as a measure of change in clinical treatment or intervention trials. In this report, we will not address whether specific GW service-related risk factors (e.g., environmental hazards) are predictive of lower current physical functioning levels, as other epidemiological studies have done.[7] Instead, our intent is to describe the health-related quality of life in a group of GW-deployed veterans and to characterize medical conditions that might contribute to decreased levels of physical functioning.

Methods

The present study was part of a larger center project (conducted between late 1994 and the spring of 1996) that studied outcomes in GW veterans approximately 4 years after their return from the GW. Upon arrival at their scheduled appointments, participants were asked to provide informed consent and were administered a study protocol that included two questionnaires, an environmental interview, a neuropsychological test battery, and standardized, structured psychiatric interviews.

Participants

Participants in the current study were recruited from a New England-area cohort that included 2,949 U.S. Army members (active duty, reserve, and National Guard) from more than 70 different units who returned from GW deployment through Fort Devens, Massachusetts.[24–26] The cohort is largely male (92%), white (83%), and from the National Guard component (52%). Thus, in some respects, it differs from the troop duty status and ethnic breakdown of the total U.S. Persian Gulf force, which was 50% active duty, 16% reserve and National Guard, and 68% white.[27]

Because we were concerned that persons with more health complaints might be more likely to participate if we recruited cohort members randomly, we used a stratified random sampling strategy to select a study subject pool with an equal representation of higher and lower physical health symptom reporters from the larger study cohort and to ensure the inclusion of comparable numbers of women and men. (For further descriptions of the subject group and the sampling methodology, see Proctor et al.[9] and Wolfe et al.[28]) Using this procedure, a sample of 353 troops from the larger Fort Devens cohort was identified for participation; 220 persons (62%) agreed to participate in the study, representing 84% of those who could be located and contacted. Of the 220 Fort Devens cohort participants, 148 were able to complete the entire study protocol; the remaining 72 individuals now lived outside the New England area and could not complete the in-person interviews and cognitive testing. Of the 133 nonparticipants, 88 could not be located and 45 did not participate for other reasons (i.e., deceased [$N = 4$], refused [$N = 4$], did not appear at scheduled appointment times or would not commit to a testing date [$N = 37$]).

A U.S. Army National Guard air ambulance unit, activated and sent overseas to Germany during the GW (December 1990 to August 1991), was recruited to serve as a comparison group. This unit consisted of a range of military occupational specialties, including medics, helicopter pilots, flight crews, mechanics, communications specialists, and administrative support personnel. The unit's intended mission was the handling and transport of wounded U.S. soldiers evacuated from the GW. Because of low U.S. casualties, however, the unit actually assisted German civilian evacuation and transport missions. Fifty Germany-deployed veterans (85% of those who could be located and contacted; 51% of the deployed unit) participated in the study in the spring of 1995.

The current report focuses on the SF36 and medical and psychiatric status data for those GW-deployed and Germany-deployed participants who were able to participate in the entire study protocol and for whom there were complete data for all of the covariates of study (i.e., 141 of the 148 GW-deployed group and 46 of the 50 Germany-deployed group).

Measures

Data in the analyses were drawn from the questionnaires and the psychological interview.

Demographic Factors, Disability Status, and Personality

Information about a number of demographic variables was collected via questionnaire, including age (in years), education level (in years), sex, race, current marital status, employment status, military status during GW service, and prior military service history. Several other variables related to functional health (such as disability status) or known to affect self-reported assessment of health or physical symptoms (personality traits) also were examined. Whether the subject was on current disability, seeking a disability rating, and/or seeking an upgrade to a current rating was queried by questionnaire. To assess trait personality, a short, 27-item version of the Eysenck Personality Inventory[29] called the EPI-Q[30] Form B was administered. Summary scores indicating emotionality (neuroticism), extroversion, and tendency toward "faking good" responses were calculated according to established criteria.

SF36

The SF36 is a well-validated tool for the measurement of functional status.[15,16] The 36 items of the scale comprise eight

subscales (Physical Functioning, Role-Physical, Bodily Pain, Vitality, General Health, Social Functioning, Role-Emotional, and Mental Health) and two summary scores (Physical Component Summary [PCS] and Mental Component Summary [MCS]) based on established scoring algorithms. For the subscales, transformed scores range from 0 to 100, where the maximum score indicates no impairment. Extensive examination of the psychometric properties (validity, reliability, and precision) of the SF36 has been performed. In previous research, the eight subscales have been found to form two distinct clusters,[16] with the Physical Functioning, Role-Physical, and Bodily Pain subscales contributing most to the PCS measure and the Role-Emotional and Mental Health subscales contributing most to the MCS measure. The Vitality, General Health, and Social Functioning subscales correlate with both summary measures. The General Health subscale correlates most highly with the physical component and thus is included in calculating the PCS; the Social Functioning subscale correlates most highly with the mental component and is included in calculating the MCS; the Vitality subscale correlates with both but is included in the MCS component.

For the current data, the internal consistency reliability of the individual items that make up the subscales was good to excellent (α ranging from 0.62 for Mental Health to 0.88 for Physical Functioning). The internal consistency reliability of the subscales used to determine the two summary measures was good, with $\alpha = 0.82$ for the PCS and $\alpha = 0.74$ for the MCS.

Because we did not administer the full SF36 to all participants initially, approximately 40 people in the GW-deployed group (28%) did not complete the Vitality, Social Functioning, Role-Emotional, and Mental Health subscale items. These 40 people did not differ on any demographic characteristics, medical conditions, or psychiatric disease status from the other 100 persons. Thus, these data were assumed to be missing completely at random. To include these subjects' data in the analyses, we imputed data for the specific missing questionnaire responses using the expectation-maximization missing value algorithm within SPSS.[31] Imputed values were based on the age, education, and gender characteristics of the subjects.

Medical Conditions

For the present analyses, subjects were considered to have a current medical condition if they reported any 1 of 13 medical conditions: a doctor's diagnosis of hypertension, a heart attack in the last year, other heart trouble or circulatory problem, diabetes, or cancer (except skin); or current complaints of chronic allergies or sinus troubles, arthritis of any kind or rheumatism, sciatica or chronic back problems, blindness or trouble seeing with one or both eyes, chronic lung disease (such as bronchitis, asthma, or emphysema), chronic skin rash, deafness or other trouble hearing, or limitation in the use of an arm or leg (because the limb was missing, paralyzed, or weak). These conditions were among those considered in the 1990 National Survey of Functional Health Status,[32] a survey of 2,474 noninstitutionalized U.S. adults (43% male, 28% older than 65 years) from which general U.S. population norms for the SF36 were determined and have been published.[15,16]

Psychiatric Status

Subjects were considered to have a psychiatric disorder if they were diagnosed with a current psychiatric disorder by the clinical diagnostic interviews described below.

(i) Post-Traumatic Stress Disorder (PTSD). The Clinician Administered PTSD Scale (CAPS), a structured clinical interview designed to assess clinical levels of PTSD, was administered to all participants by one of two trained, doctoral-level clinicians. The psychometric properties of the scale are well established, with both high reliability and validity.[33] In addition to the clinical interview, all participants completed the Mississippi Scale[34] adapted for use in Persian Gulf War veterans. The Mississippi Scale is a 35-item paper-and-pencil scale designed to measure PTSD symptoms. The psychometric properties of the Mississippi Scale are well established, and the reliability in the current sample was quite good ($\alpha = 0.92$).

(ii) Axis I Psychiatric Diagnoses. Participants also were administered the Structured Clinical Interview for DSM-III-R [Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised], Non-Patient Edition (SCID),[35] by one of two trained, doctoral-level clinicians. The SCID is a structured clinical interview designed to assess both current (within the last month) and lifetime (at any time including currently) axis I disorders. Past research shows that the SCID has acceptable joint interrater reliabilities, with κ values ranging between 0.70 and 0.94. For the current study, all portions of the interview were administered except the sections on substance use disorders and PTSD, because these were screened through other methods. In addition to the clinical interview, all participants completed the Brief Symptom Inventory (BSI).[36] In these analyses, we examined the General Severity Index from the BSI as a measure of general psychological symptomatology.

Interrater reliability for the PTSD diagnosis and specific axis I diagnoses on a selected subset of 24 of the 148 combined CAPS and SCID structured interviews was excellent ($\kappa = 1.00$). Overall, in this group, there was a low number of persons with positive diagnostic interviews[28]; thus, half of the interviews initially selected for the reliability analyses were positive for a diagnosis of at least one disorder.

Measure of Motivation

The Test of Memory Malingering was administered to all study subjects starting in the spring of 1995; thus, test performance scores are available for 56 of the GW-deployed subjects and all 46 of the Germany-deployed group. This is a simple 50-item visual memory test assessing the inclination to malinger or embellish memory deficits; it has been well validated in numerous neurologic patient groups as well as in normal control populations who were asked to feign poor performance.[37]

Record Review

Medical records for the 57 GW-deployed persons who indicated that they had participated in the DVA's GW Registry examination and who gave consent for their charts to be reviewed were requested from DVA Medical Records. We targeted participants who had a GW Registry examination for the record review process because we assumed that they would be most likely to have a DVA medical record. A total of 20 (35%) of these individuals' records were located when requested in January 1999.

Each chart was reviewed by a doctoral-level clinician, and any doctor-corroborated medical condition indicated in the charts as occurring between or estimated to have occurred between the date of the veteran's return from GW deployment and the date of study participation was considered. Specific, individual conditions indicated as present in the medical records were then compared with veterans' self-reported study information on the questionnaire and clinical interview (for psychiatric conditions). Validity measures (percent agreement and κ statistics) were calculated.

Statistical Analyses

The sample was weighted to account for the sampling design and the response rates across sampling strata (i.e., high and low symptom reporters) so that the sample more accurately reflected the gender and symptom distribution of the larger Fort Devens population participating in the earlier study phase. The SUDAAN statistical package[38] was used to perform the analyses weighted for the sampling design. All of the results presented in the tables reflect these weighted-for-sampling-design analyses. For the comparison of demographic factors, health, and rates of psychiatric diagnoses by sample (GW deployed vs. Germany deployed), pairwise comparisons of means were based on a modified t test and pairwise comparisons of percentages were based on a modified χ^2 test in SUDAAN. We used a two-sample Student's t test to compare the SF36 mean scores for the Fort Devens group with those published for a general U.S. population sample.[15,16] For comparison of the SF36 subscale and summary scores by medical and psychiatric diagnosis status within the GW-deployed group, an overall comparison of the differences across the three groups was performed. (The three diagnostic status groups were those with no medical conditions or psychiatric disorders, those reporting at least one medical condition but no current psychiatric diagnosis, and those with a current psychiatric diagnosis.)

Multiple linear regression analyses were performed to examine the risk factors associated with lower physical health functioning within the GW-deployed group. The PCS score and the Physical Functioning subscale score were the outcomes of interest. Three different models were run. In the first model, the following variables were entered: age, years of education, sex, current disability, seeking a disability rating, history of an alcohol problem, type of service duty in the Persian Gulf (active vs. guard/reserve), current military status (civilian vs. still in the military), General Severity Index (a measure of psychological symptomatology), number of medical conditions reported, and diagnosis of any current psychiatric disorder. To examine the contribution of individual current medical and psychiatric conditions on physical functional health status, the second model included most of these variables; however, instead of the latter two variables, the six most prevalent individual medical conditions (i.e., chronic back problems, respiratory allergies, skin rash, high blood pressure, chronic lung problems, and arthritis) and the two most prevalent current psychiatric disorders (i.e., current PTSD and current major depression) were included. In the third model, the same regression models were rerun, but this time excluding those persons with any current psychiatric diagnosis. This was performed to explore the contribution of the individual medical conditions to the PCS score and the Physical Functioning subscale score in persons with no psychiatric diagnoses.

Within the GW-deployed group, all SF36 subscale and summary scores were generally normally distributed; the exception was Role-Physical, for which a large proportion of the responses were at ceiling (i.e., 50% were at 100). All SF36 measures were examined as continuous scale variables.

Results

Demographic Comparison of GW-Deployed and Germany-Deployed Groups

No significant differences between GW-deployed and Germany-deployed groups in mean years of education, sex, employment status, or marital status were observed (Table I). However, compared with the GW-deployed group, the Germany-deployed group was older and a higher percentage served in Vietnam and had remained in the military. Furthermore, a lower percentage of the Germany-deployed group was seeking a disability rating or upgrade.

Comparison of Medical and Psychiatric Status between GW-Deployed and Germany-Deployed Groups

Differences between the GW-deployed and Germany-deployed groups were noted for several individual medical conditions, with the GW-deployed group reporting significantly higher rates of hypertension and skin rash (Table I). The Germany-deployed group reported higher rates of cancer, other heart problems, arthritis, and chronic back pain, although the differences were not significant. Higher rates of psychiatric diagnoses were observed in the GW-deployed group.

Although a significant difference was noted between the GW- and Germany-deployed groups for neuroticism levels (with the mean level for the GW-deployed group being higher), there were no significant differences between the two groups in terms of extroversion, faking good responses, or motivation levels.

Comparison of Functional Health Status between the GW- and Germany-Deployed Groups and U.S. Population Norms

Figure 1 shows a graphic comparison of SF36 subscale and summary scores between the GW- and Germany-deployed groups and published general U.S. population survey norms.[15,16] Each of the mean SF36 scores was significantly lower in the GW-deployed group compared with the Germany-deployed group. The differences remained significant after controlling for age, gender, and education differences between the groups.

When comparisons were made between the mean SF36 scores for the GW-deployed group and the published general U.S. population norms, the GW-deployed group had significantly lower mean scores for the two summary scores and for all of the subscale scores except Physical Functioning. More specifically, the median scores for the GW-deployed group (Table II) were at or below the 25th percentile of the general U.S. population norms for the Bodily Pain, Social Functioning, and Mental Health subscales and the MCS score, and between the 25th and 50th percentiles for the Physical Functioning, General Health, Vitality, and Role-Emotional subscales and the PCS score.

TABLE I

DESCRIPTIVE CHARACTERISTICS OF GW- AND GERMANY-DEPLOYED GROUPS

Characteristics	GW Deployed (N = 141)	Germany Deployed (N = 46)
Demographic variables		
Age, mean years (SE) [range]	36.5 (1.0) [22–61]	40.8 (1.4) [28–56]*
≤35 years	51.2%	39.1%
Education, mean years (SE) [range]	13.4 (0.2) [9–20]	13.8 (0.2) [12–17]
≤12 years	54.2%	32.6%*
Female	8.7%	13.0%
Non-white Caucasian	4.2%	0*
Unemployed	9.0%	15.2%
Previous Vietnam service	17.2%	41.3%*
With current disability rating	11.2%	4.4%
Seeking disability rating or upgrade	12.0%	0**
Not currently married	37.9%	26.1%
Current smoker	31.8%	26.1%
Ever had alcohol problem	7.4%	7.0%
Current civilian status	31.9%	13.0%*
Personality and motivation levels		
Eysenck subscales:		
Extroversion, mean score (SE)	5.0 (0.2)	5.2 (0.3)
Neuroticism, mean score (SE)	4.5 (0.3)	3.5 (0.4)*
Lying, mean score (SE)	2.1 (0.2)	1.7 (0.2)
Test of Memory Malingering, mean score (SE)	48.0 (0.5)[a]	48.2 (0.5)
Medical and psychiatric status		
No. of medical conditions, mean (SE) [range]	1.1 (0.1) [0–7]	0.80 (0.10) [0–3]
Individual medical conditions		
High blood pressure, hypertension	13.9%	4.4%*
Heart attack	0	0
Other heart problems	2.9%	4.4%
Diabetes	2.0%	0
Cancer (excluding skin cancer)	2.1%	4.4%
Chronic respiratory allergies	16.0%	13.0%
Arthritis	10.8%	13.0%
Chronic back pain	21.4%	21.7%
Eye or vision problems	1.3%	0
Chronic lung problems	11.8%	6.5%
Skin rash	14.0%	4.3%*
Deafness or hearing problems	9.7%	6.5%
Limited use of limbs	5.5%	2.2%
Current psychiatric diagnosis	15.4%	0**
Current major depression	7.0%	0*
Current PTSD	4.4%	0*
Lifetime major depression	15.8%	4.4%*
BSI General Severity Index score, mean (SE) [range]	0.62 (0.07) [0–3.17]	0.20 (0.03) [0–0.96]**
Mississippi PTSD score, mean (SE) [range]	70.4 (2.2) [42–148]	57.4 (1.8) [40–109]**

Analyses comparing the two groups were run in SUDAAN to weight for sampling design: *$p < 0.05$, **$p < 0.001$.
[a] N = 56 in the GW-deployed group.

Comparison of Functional Health Status by Medical and Psychiatric Disorder Status within the GW-Deployed Group

Within the GW-deployed group, 53 persons (38%) had no current medical conditions or psychiatric disorders, 65 persons (46%) reported at least one medical condition but had no current psychiatric diagnosis, and 23 persons (16%) had a current psychiatric diagnosis (17 of these 23 had at least one medical condition as well). Significant differences in SF36 subscale and summary scores (except for the Vitality subscale) were noted across the three groups. The lowest mean scores (indicating lower functional health status) were reported consistently by those with a current psychiatric diagnosis (Table III). There were no significant differences in mean scores for extroversion, neuroticism, tendency toward lying, or motivation levels in overall comparisons between these three groups. However, the group with psychiatric conditions had a significantly higher mean neuroticism score compared with the group with no medical or psychological conditions.

Predictors of Physical Functional Health Status within the GW-Deployed Group

Multiple linear regression models examining the risk factors associated with lower PCS and Physical Functioning scores in the GW-deployed group indicated that lower education levels,

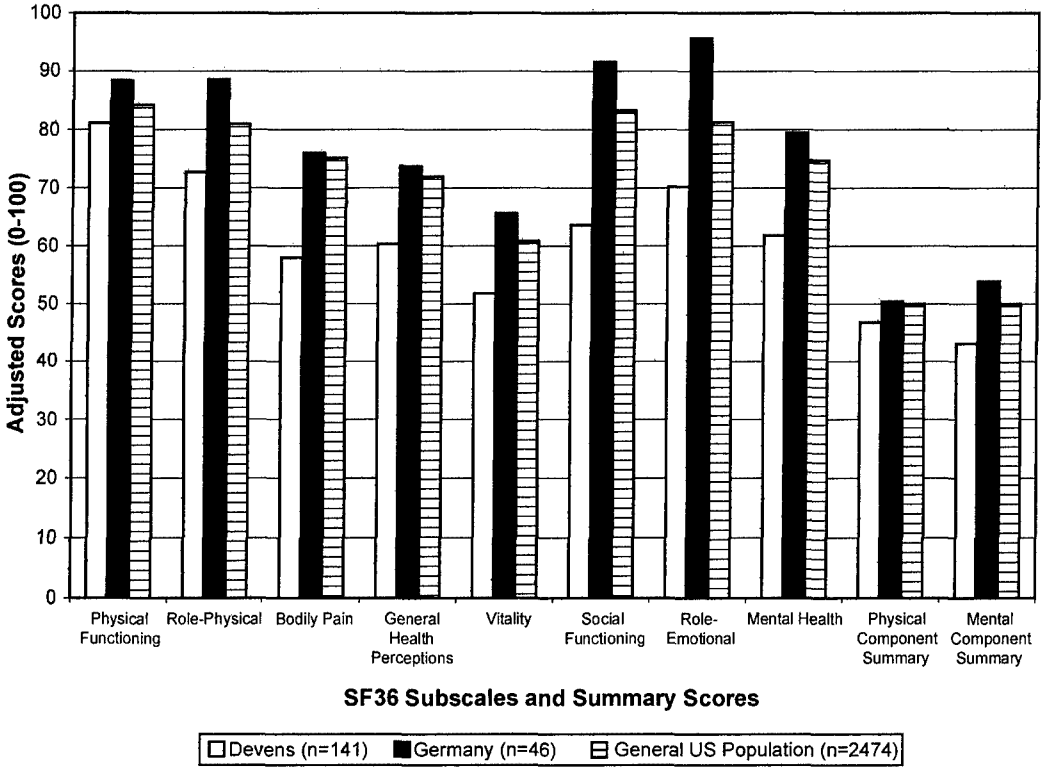

Fig. 1. Comparison of SF36 scale scores between groups and U.S. population means.

TABLE II

SF36 SUBSCALE AND SUMMARY SCORES FOR GW-DEPLOYED FORT DEVENS COHORT

	Physical Functioning	Role-Physical	Pain Index	General Health	Vitality	Social Functioning	Role-Emotional	Mental Health	Physical Component	Mental Component
Mean	81.1	72.1	58.0	60.3	51.8	63.6	70.2	61.8	46.8	43.1
25th percentile	66.0	34.7	36.6	49.3	40.0	36.3	58.4	49.0	40.0	37.7
50th percentile (median)	89.7	100.0	61.4	61.2	50.0	62.3	73.3	60.6	49.9	42.7
75th percentile	100.0	100.0	73.2	71.7	61.5	82.4	100.0	73.3	53.3	49.7
SE	2.3	3.4	2.4	2.2	2.0	2.8	3.3	2.0	0.95	1.0
Range	15–100	0–100	0–100	0–100	0–90	0–100	0–100	16–100	17.7–66.5	18.1–63.9

N = 141. Mean age, 36.5 years; >35 years, 48.8%; female, 8.7%; mean education, 13.4 years; white, Caucasian, 95.8%. Five most prevalent comorbidities: chronic back problems, 21.4%; respiratory allergies, 16.0%; any current psychiatric diagnosis, 15.4%; skin rash, 14.0%; chronic lung problems, 11.8%.

higher levels of psychological symptomatology, and a higher number of chronic medical conditions reported were significant risk factors (Table IV, model I). Across all of the models, each additional year of education predicted a 1- to 2-point higher (or better) PCS or Physical Functioning subscale score in this study cohort. Examination of the effects of individual medical and psychiatric conditions (Table IV, model II) on the PCS score showed that having chronic back pain predicted a 4-point lower summary score, respiratory allergies predicted a 3-point lower score, and chronic lung problems and arthritis each predicted a 5-point lower score. A current diagnosis of PTSD or major depression was associated with a PCS score that was 10 to 12 points lower. In addition to a current diagnosis of PTSD or major depression, chronic lung problems and arthritis were significant medical predictors of a lower Physical Functioning subscale score. Additional regression analyses (not shown) found that about one-third of the total model variance in both the PCS and Physical Functioning subscale scores was explained by the addition of the variables for the two psychiatric diagnoses to the models (i.e., for the PCS, the model adjusted R^2 was 0.29 without these two variables and 0.41 when the variables were included).

When only those persons without a current psychiatric diagnosis were included in the regression model (Table IV, model III; N = 118), the important medical predictors for both outcomes were similar to those described in model II, with similar unstandardized β coefficients. The adjusted model R^2 indicated that demographic variables and current medical conditions explained 29% and 25% of the variance in the PCS and Physical Functioning subscale scores, respectively.

Record Review Validation

Overall, the level of agreement between the information recorded during the study and that recorded in the medical

TABLE III

COMPARISON OF FUNCTIONAL STATUS BY MEDICAL AND PSYCHIATRIC DISORDER STATUS WITHIN THE GW-DEPLOYED GROUP

	No Medical or Psychological Conditions (n = 53)	Medical but No Psychological Conditions (n = 65)	With Psychological Conditions (n = 23)	Overall Comparison of Groups
Physical functioning	89.0 (3.3)	79.1 (3.5)	67.2 (5.2)	$p = 0.002$
Role-physical	85.0 (4.4)	65.5 (5.4)	59.9 (8.3)	$p = 0.005$
Bodily pain	66.8 (3.0)	57.4 (3.2)	37.6 (6.3)	$p < 0.001$
General health perceptions	66.3 (2.3)	59.0 (3.8)	49.1 (6.0)	$p = 0.02$
Vitality	51.5 (2.5)	54.3 (3.0)	45.4 (5.0)	NS
Social functioning	68.4 (3.9)	66.3 (4.3)	43.7 (6.3)	$p = 0.003$
Role-emotional	78.5 (3.7)	67.5 (5.2)	57.9 (8.8)	$p = 0.04$
Mental health	61.6 (2.6)	66.2 (3.2)	49.2 (3.5)	$p = 0.002$
PCS score	51.0 (1.3)	45.1 (1.4)	41.0 (2.6)	$p < 0.001$
MCS score	43.0 (1.5)	45.0 (1.7)	37.7 (2.2)	$p = 0.05$

All group comparisons were additionally adjusted for age, gender, and education in SUDAAN; the adjusted mean scores (SE) are presented.
NS, not significant.

records was generally considered low to moderate, according to the criteria of Landis and Koch.[39] The percent agreement between the two sources was between 85% and 100% for 9 of the 13 individual medical conditions and the presence of a psychiatric diagnosis. Within the 20 individuals studied, there were no positive diagnoses for 4 of the medical conditions (heart attack, other heart problems, diabetes, and respiratory allergies). So, although technically there was 100% agreement, κ statistics could not be determined for these four conditions. The κ statistics that could be determined ranged between 0.35 and 0.64. The exceptions were for arthritis, chronic back problems, and limb limitations, for which the κ values were quite low (<0.10).

Discussion

Confirming other epidemiological studies comparing SF36 scores in GW-deployed and nondeployed veterans,[3,7] we found that GW-deployed veterans had significantly lower functional health status than a Germany-deployed comparison group. Despite our hypothesis that GW-deployed veterans would have better physical functional health because of selection and training characteristics, we found that this group of New England-area GW-deployed veterans reported lower functional health status than published general U.S. population norms. One could argue that the general U.S. population sample we used for comparison purposes was not age and demographically matched to our GW-deployed group, because it included older age groups, a higher percentage of women, and persons with various levels of medical illness. However, these are factors that would suggest that the general U.S. population norms would be lower than those in our GW-deployed group. Our Germany-deployed comparison group reported mean levels higher than the general U.S. population.

It is important to note that our results may not be readily generalizable to the total U.S. GW force, because our study cohort was exclusively U.S. Army and included a high proportion of National Guard/Army Reserve troops. Still, review of our SF36 results shows strong comparability with findings from two large epidemiological study samples of GW veterans from the United States[3] and the United Kingdom.[7] The mean SF36 subscale scores in this GW-deployed population were higher than levels typically reported by DVA ambulatory veterans seeking care[18] as well as other civilian and military ambulatory care patients.[40]

One interesting finding was the large mean difference in SF36 scores when they were evaluated across the three medical and psychiatric diagnosis status groups of the GW-deployed veterans (Table III). We found 10- to 30-point differences on the subscale scores, especially those more related to physical functioning, and 5- to 10-point differences for the summary scores. These results indicate that there is considerable variation in the functional health status of these GW veterans, as might be expected from a group that includes individuals with varying degrees of health problems. It is important to point out that other factors besides formal clinical medical or psychiatric problems may contribute to the variation in functional health status in this group. We examined the rates of chronic multisymptom illness (CMI; defined by Fukuda et al.[5] as reporting at least one symptom from two of three different symptom clusters: fatigue, mood and cognition, and musculoskeletal) across these three diagnostic status groups. Although we found that 71% of those with only current medical conditions and 91% of those with psychiatric diagnoses met the criteria for CMI, 55% of the subjects with no medical or psychiatric conditions also met the health symptom-based case criteria for CMI. (The mean PCS score for subjects with no medical or psychiatric conditions but meeting the case criteria for CMI was 48.6 [SE = 1.7]).

As reflected in the regression results (Table IV, model I), higher numbers of medical conditions and psychological symptomatology appear to be important predictors of poorer physical functioning in this GW-deployed group. Increased psychological symptomatology is an expected predictor of reduced functional health status, given the robust association of psychological symptomatology with somatic complaints in numerous civilian and veteran populations.[41,42] However, because of the cross-sectional nature of this study, it was not possible to determine the directionality of this association: increased psychological symptomatology, for example, may result in reports of poorer health status. But the converse is also true: poorer health status can lead to increased symptomatology. Other studies[18,43] have examined medical predictors of physical functioning quality-of-life outcomes and found comparable results in terms of the

TABLE IV

MULTIVARIATE LINEAR REGRESSION MODELS PREDICTING PCS AND PHYSICAL FUNCTIONING SUBSCALE SCORES IN THE GW-DEPLOYED GROUP (N = 141)

	PCS			Physical Functioning Subscale		
	Model I	Model II	Model III	Model I	Model II	Model III
Age	−0.11	−0.08	−0.11	−0.36	−0.28	−0.32
Years of education	0.75*	1.2**	0.97*	1.3	2.3*	1.9†
Female (1)	0.98	1.6	0.58	2.5	3.3	0.69
Current disability rating (1)	1.9	0.21	−0.94	3.5	4.9	5.0
Seeking a disability rating (1)	−1.5	1.4	3.2	−2.8	2.5	0.78
History of alcohol problem (1)	−2.6	1.6	11.3†	−1.5	7.2	26.9
Active duty service in the GW (1)	2.7	3.1	0.02	0.92	3.7	1.1
Currently on civilian status (1)	−1.6	−1.3	−0.57	0.54	4.3	5.8
GSI from the BSI	−5.5**			−12.8**		
No. of medical conditions (0–13)	−2.1**			−3.7*		
Any current psychiatric diagnosis (1)	−1.6			−4.7		
Chronic back problems (1)		−4.1*	−4.2†		−3.4	−3.1
Respiratory allergies (1)		−3.1†	−3.1		−4.2	−4.2
Skin rash (1)		−0.28	−1.8		4.2	0.88
High blood pressure (1)		−0.47	0.34		4.5	5.1
Chronic lung problems (1)		−5.3†	−6.1*		−18.1*	−21.3**
Arthritis (1)		−5.3†	−5.2†		−12.3†	−13.1*
Current PTSD (1)		−11.9**			−15.7*	
Current major depression (1)		−10.2**			−30.4**	
Adjusted R^2	0.44	0.41	0.29	0.37	0.37	0.25

Unstandardized coefficients are denoted. Numbers in parentheses in the first column indicate coding of variables (where 1 equals yes for dummy variables).

Model I: Forced entry of the variables age, education, female, current disability, seeking a disability rating, history of an alcohol problem, service duty in the Persian Gulf (active vs guard/reserve), psychological symptomatology as measured by the General Severity Index (GSI) of the BSI, number of medical conditions reported, and diagnosis of any current psychiatric disorder.

Model II: Forced entry of same variables in model I, except instead of the latter two variables, the six most prevalent individual medical conditions and the two most prevalent current psychiatric disorders were included.

Model III: Forced entry of all variables included in model II, excluding those subjects with any current psychiatric diagnosis (n = 118 included).

Note: For format clarity, the SE and 95% confidence intervals are not presented for each of the model coefficients; these are available from the authors on request.

†$p < 0.10$; *$p < 0.05$; **$p < 0.01$.

levels of effect for various individual medical conditions, but those studies did not simultaneously address the contribution of psychiatric diagnoses or psychological symptomatology. Results from this study suggest that about 30% of the total model R^2 for outcomes encompassing levels of physical functioning is explained by psychiatric diagnoses.

Certainly, one limitation of this study is its reliance on self-report measures. However, we used well-validated and documented assessment tools to assess functional health outcomes (SF36) and psychiatric diagnoses (CAPS and SCID), conducted simultaneous assessment of the tendency to exaggerate and of motivation levels, and attempted to address recall and response biases regarding the self-reported medical conditions by means of medical record review. Recently, negative affectivity (defined as a general personality trait to experience subjective distress and measured by the Eysenck neuroticism score) has been found to be negatively correlated with reported health-related quality-of-life measures.[44] We found that the addition of the neuroticism score to our regression model I explained little additional variance in the physical functional status domains we investigated, perhaps because we simultaneously controlled for psychological symptomatology (by including the General Severity Index of the BSI).

The medical record review in this GW-deployed group indicated low to moderate agreement between sources for most medical conditions and psychiatric diagnoses from clinical interviews. One possibility for the relatively low agreement is that the low numbers of persons with these conditions limits estimates of reliability.[45] Another methodological explanation for the poor validation of these conditions (noted during the chart review phase) may be the relatively inconsistent reporting in the medical records of the dates when these chronic physical conditions occurred. Several studies have explored possible individual-level characteristics that might explain discordance between self-reporting of medical conditions on questionnaires and medical records,[46,47] but in summary, the discrepancies appear to be condition specific. As might be expected, more accurate reporting is more likely for diseases that have clear diagnostic criteria.[48] Additionally, a recent study suggested that self-reported information from more educated persons is better than that from less educated persons when examining chronic lung disease, heart disease, and diabetes.[49]

Another potential limitation of this study is the relatively small sample size given the number of risk factors of interest (i.e., demographic factors, individual medical conditions, and psychiatric diagnoses). However, this study was primarily an exploration of the predictors that play a clinical role in predicting lower functional status. Given the sample size, this study

had sufficient power to detect differences of at least 5 to 10 points on the individual subscales and of 2 to 5 points on the summary scales between the GW-deployed group and the general U.S. population norms (assuming $\alpha = 0.05$ by two-tailed test, power = 80%[15,16]). These differences are typically indicative of clinically meaningful changes in functional status.

Other possible risk factors for lower functional health status described in the literature, but not evaluated directly in this study, are lower socioeconomic status (SES),[50,51] lower social support,[52] and current job strain,[53] which is defined as high work demands with low control over those demands.[54] Education level (which in our study was a significant predictor of better functional health status) is sometimes used as a surrogate measure of SES; however, as indicated above, there may be other biases in using education level as a predictor. Unemployment status (as a proxy for SES) and marital status (as a proxy for social support) were entered as covariates in the preliminary models, but these did not contribute to the overall model.

Assessment of health and well-being as it affects one's daily life is becoming an increasingly informative mechanism for monitoring clinical health.[55] The DVA is currently testing several treatment regimens to determine their effectiveness in improving physical functioning in symptomatic GW veterans.[10,11] These efforts, coupled with the initiation of other surveillance mechanisms for data collection of functional health status measures, are likely to help better characterize health-related quality of life in military personnel at baseline and in veterans over time.

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